NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Blueprint Medicines

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. GIST Cancer UK (also known as GIST Support UK)
   b. Sarcoma UK

4. Expert personal perspectives from:
   a. Dr Charlotte Benson, clinical expert nominated by Sarcoma UK
   b. Dr V Ramesh Bulusu clinical expert nominated by GIST Cancer UK

5. **Evidence Review Group report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical Report**

8. **Technical engagement response** from Blueprint Medicines

9. **Technical engagement responses from experts:**
   a. Dr Charlotte Benson, clinical expert nominated by Sarcoma UK

10. **Technical engagement response from consultees and commentators:**
    a. NCRI-ACP-RCP-RCR

11. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

12. **Post technical engagement submission of additional evidence** from Blueprint Medicines

13. **Evidence Review Group critique of company additional evidence** prepared by prepared by Southampton Health Technology Assessments

Centre (SHTAC)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Document B

Company evidence submission

April 2020

File name	Version	Contains confidential information	Date
		Yes	

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This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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In this template any information that should be provided in an appendix is listed in a box.

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Tables and figures

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorization for this indication.

The decision problem addressed by this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (*PDGFRA*) D842V mutation regardless of prior therapy.	[redacted]	This is the population for which avapritinib is anticipated to receive its marketing authorisation from the EMA and is in line with the evidence presented in the pivotal clinical trial; the NAVIGATOR study.
Intervention	Avapritinib	Avapritinib	Not applicable
Comparator(s)	• Imatinib (for adults who have KIT [CD117]-positive tumours) • Sunitinib (for adults whose treatment with imatinib has failed due to resistance or intolerance) • Regorafenib (for adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib) • Established clinical management without avapritinib including best supportive care	Established clinical management without avapritinib including: • Imatinib • Sunitinib (for adults whose treatment with imatinib has failed due to resistance or intolerance) • Regorafenib (for adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib) • Best supportive care	The appropriate comparators have been selected for the anticipated licensed population for avapritinib in line with clinical opinion.
Outcomes	The outcome measures to be considered include: • Overall survival • Response rate (including partial response rate and duration of response) • Progression-free survival • Adverse effects of treatment	The outcome measures to be considered include: • Overall survival • Response rate (including partial response rate and duration of response) • Progression-free survival • Adverse effects of treatment	Time on treatment is an important outcome of interest for use in the economic model, as tracking patient outcomes via line of therapy avoids the issue of noncomparability of progression across treatments

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life	• Health-related quality of life • Time on treatment	
Economic analysis	• The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account • The use of avapritinib is conditional on the presence of the *PDGFRA* D842V mutation. The economic modelling should include the costs associated with diagnostic testing for the *PDGFRA* D842V mutation in people with unresectable or metastatic GIST who would not otherwise have been tested. A sensitivity analysis should be provided without the	• The cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year • The time horizon runs until over 99% of patients have died in both treatment arms • Costs are considered from an NHS and Personal Social Services perspective • Where known, commercial arrangements for the intervention, comparator and subsequent treatment technologies are taken into account • The clinical evidence is based only on eligible (i.e. metastatic or unresectable) patients with the *PDGFRA* D842V mutation	According to clinical experts, nearly all patients will have their mutational status known before or within three weeks of diagnosis with unresectable or metastatic GIST.[1]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals		
Key: EMA, European Medicines Agency; GIST, gastrointestinal stromal tumour; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; KIT, v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; *PDGFRA*, platelet-derived growth factor receptor alpha.			

B.1.2. Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

A summary of avapritinib is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Avapritinib (AYVAKYT™)
Mechanism of action	Avapritinib is a Type 1 tyrosine kinase inhibitor that binds to the active conformation and inhibits a broad range of *PDGFRA*- and *KIT*-mutant kinases at clinically relevant concentrations.[2] 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) and *KIT* exon 11, 11/17 and 17 mutants (d557-558, V560G, V560G/D816V, V560G/N822K, D816E, D816F, D816H, D816I, D816V, D816Y, D820E, D820Y, and Y823D), sparing activity on a range of other kinases including VEGFR2. Avapritinib has demonstrated biochemical in vitro activity on the *PDGFRA* D842V and *KIT* D816V mutants,[2] associated with resistance to imatinib, sunitinib and regorafenib – with IC50 values of 0.24 nM and 0.27 nM, respectively, and greater potency against clinically relevant *KIT* exon 11 and *KIT* exon 17 mutants than against the *KIT* wild-type enzyme. In in vitro cultured cells and in vivo tumour models, avapritinib demonstrated potent on-target inhibition of *KIT* exon 17-mutant signalling, inhibition of cellular proliferation, and apoptotic induction in *KIT* exon 17 mutant cell lines.
Marketing authorization status	[redacted] Avapritinib was granted orphan designation by the EMA for the treatment of GIST on 14 August 2017.[3] On 9 January 2020, the FDA approved avapritinib for adults with unresectable or metastatic GIST harbouring a *PDGFRA* exon 18 mutation, including

	the D842V mutation.[4] The FDA granted this application priority review and Breakthrough Therapy designation. Avapritinib also received fast track and orphan drug designations from the FDA.[4]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated MA for avapritinib for this indication is: [redacted]
Method of administration and dosage	300 mg orally, once daily. The dose should be adjusted based on safety and efficacy. Treatment should be continued until disease progression or unacceptable toxicity.
Additional tests or investigations	According to clinical opinion obtained by Blueprint Medicines,[1, 5] and in line with current guidelines,[6-8] mutational testing is performed as standard practice for patients diagnosed with GIST. Therefore, no additional tests or investigations would be required to identify patients with the *PDGFRA* D842V mutation, who would be eligible for avapritinib, beyond what is already performed in standard clinical practice in England and Wales.
List price and average cost of a course of treatment	List price: £26,666.67 per bottle; average cost of a course of therapy (PAS price) [redacted].
Patient access scheme (if applicable)	A simple confidential discount PAS for avapritinib of [redacted] has been proposed. The avapritinib expected PAS price per bottle of 30 tablets (100 mg, 200 mg or 300mg) is [redacted].

Key: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GIST, gastrointestinal stromal tumour; IC50, half-maximal inhibitory concentrations; KIT, v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MA, marketing authorization; MAA, marketing authorization application; NHS, National Health Service; PAS, patient access scheme; *PDGFRA*, platelet-derived growth factor receptor alpha; VEGFR2, vascular endothelial growth factor receptor 2.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

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.[9, 10] 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.[11] 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.[12]

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).[13, 14] 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 with the *PDGFRA* D842V mutation – is the population for which Blueprint Medicines has submitted its marketing authorization application (MAA) to the European Medicines Agency (EMA) for avapritinib (AYVAKYT™), and this is the indication for which avapritinib is anticipated to receive its licence. Therefore, this population is the focus of this submission.

As a result of resistance to existing TKIs, patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation have a poor prognosis, with expected survival of approximately 13–15 months.[15-17] 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 overall survival (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 *PDGFRA* D842V-mutated GIST.

B.1.3.2. Clinical presentation and burden of disease

GISTs may be asymptomatic (approximately 18% of cases), especially in the case of smaller tumours of the intestinal tract.[19, 20] 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.

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,[19] 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.[21] 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.[22] It has a negative impact on health-related quality of life (HRQL) and can even lead to disability.[23] 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.[21] These patients also reported significantly worse levels of

independence, as captured by the Self-Efficacy Scale (SES).[21] Fatigue has also been associated with a number of psychological conditions, such as depression, anxiety, stress and catastrophizing.[21, 24-28]

The HRQL 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) appraisal of imatinib, it was accepted that patients with unresectable or metastatic GIST receiving imatinib at first line have a utility value of 0.935;[29] at second line, patients receiving sunitinib have a utility value of 0.781;[30] at third line, patients receiving regorafenib have a utility value of 0.767;[31] and patients with progressive disease who have exhausted all treatment options have a utility value of 0.647.[31] Clinicians agreed that these values were reflective of the HRQL of patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation in UK clinical practice.[1] 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 with current TKIs and will therefore progress quickly through each line of treatment.

Patients with GIST have also been demonstrated to experience high levels of fear relating to cancer recurrence or progression,[32] 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 therefore faster disease progression and limited expected survival, resulting in even higher levels of fear and distress for these patients (although there are currently no available data formally exploring this issue to our knowledge).

Given the high median age at diagnosis and the potential for reduced levels of physical functioning and independence of GIST patients, there will also be an associated impact on caregivers. Some caregivers for patients with GIST have been shown to experience a substantial burden, with significantly reduced mental health, less vitality, lower general health, high levels of distress, significantly lower social functioning and more role, physical and emotional problems.[33] 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 indications. For caregivers of patients with amyotrophic lateral sclerosis (ALS), 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".[34] Given that these concerns are similar to those for patients with *PDGFRA* D842V-mutated GIST, it is reasonable to assume that the effects will also be similar.

Overall, patients with GIST experience a substantial burden from their disease, which has a significant negative impact on their HRQL. This has been demonstrated to be worse for patients with unresectable or metastatic disease, who will be facing 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 as their disease progresses faster, their caregivers are also more likely to face additional burden and distress, with a significant impact on their HRQL.

B.1.3.3. Clinical pathway of care

The gold standard of treatment for GIST is surgical resection, preferably through laparoscopy if possible, or with open laparotomy if the patient is unstable.[35] In patients with GIST without metastatic disease and for whom resection is possible, resection is performed with curative intent.[36] Following surgery for KIT (CD117)-positive GISTs, as defined by the criteria outlined by Miettinen and Lasota,[9] NICE recommends imatinib as an option for adjuvant treatment for up to three years, for adult patients who are at a high risk of relapse.

Following progression to unresectable or metastatic disease, there is a very clear treatment pathway for GIST patients in England and Wales, with NICE recommending imatinib in first line followed by sunitinib in second line and regorafenib in third line. However, this treatment pathway is ineffective for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation as their disease is insensitive to these existing TKI therapies.[15]

B.1.3.3.1. Clinical guidelines for patients with unresectable or metastatic GIST with the PDGFRA D842V mutation

There are no treatments currently available that are specifically recommended for use in patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation. The British Sarcoma Group (BSG), The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines all emphasize the importance of mutational testing, prior to starting treatment, to identify those patients whose disease is insensitive to standard TKI therapy such as imatinib, sunitinib and regorafenib (including patients with the *PDGFRA* D842V mutation) (Table 3).[6-8] This is particularly specified for patients with local/locoregional GIST, where surgical resection is the gold-standard treatment and patients with the *PDGFRA* D842V mutation generally have a better prognosis. The recommendation is that imatinib should not be used in the adjuvant setting for patients with the *PDGFRA* D842V mutation. Current TKI therapies are not excluded from the recommendations for patients with the *PDGFRA* D842V mutation who progress to unresectable or metastatic disease, although patients with the *PDGFRA* D842V mutation will still be insensitive to these treatments. However, no alternative treatments are currently available for these patients, with the only recommendation in the guidance being to consider enrolment in clinical trials of new agents under investigation. A summary of the guidelines from the BSG, ESMO and the NCCN is presented in Table 3.

Table 3: Summary of guidelines for advanced or metastatic GIST patients with the *PDGFRA* D842V mutation

Guideline (year)	Guidance for patients with advanced/metastatic GIST with the *PDGFRA* D842V mutation
British Sarcoma Group (2017)[6]	No recommendations for patients with the *PDGFRA* D842V mutation. The guidelines emphasize the importance of mutational analysis at diagnosis prior to treatment to identify mutations such as D842V, which it notes are insensitive to imatinib and sunitinib. However, it does not provide alternative treatment options for patients once they reach the unresectable or metastatic disease stage. The guidance for patients who have failed imatinib, sunitinib and regorafenib is to be considered for participation in clinical trials of new agents.

Guideline (year)	Guidance for patients with advanced/metastatic GIST with the *PDGFRA* D842V mutation
ESMO (2018)[7]	Patients with the *PDGFRA* D842V mutation are generally insensitive to imatinib[37] and other TKIs and are, therefore, candidates for clinical studies on new agents targeting this mutation.
NCCN (2018)[8]	Guidance is for soft-tissue sarcoma; limited discussion is provided specific to GIST. There are no specific recommendations for management of the *PDGFRA* D842V mutation patients. Dasatinib is presented as a possible treatment for GIST patients with the *PDGFRA* D842V mutation following disease progression after imatinib, sunitinib and regorafenib. This is based on an abstract presented in 2011.[38] Dasatinib is not approved for use in the UK.
Key: ESMO, European Society of Medical Oncology; GIST, gastrointestinal stromal tumour; NCCN, National Comprehensive Cancer Network; *PDGFRA*, platelet-derived growth factor receptor alpha.	

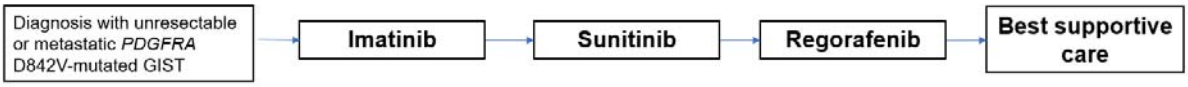
B.1.3.3.2. Clinical pathway for patients with unresectable or metastatic GIST with the PDGFRA D842V mutation

As chemotherapy and radiation are ineffective, the current treatment paradigm for metastatic or unresectable GIST involves sequential administration of the TKIs, imatinib (first line), sunitinib (second line) and regorafenib (third line).[7, 8] These agents are all indicated and approved for use in all patients with advanced GIST, regardless of mutational status. As discussed above, patients with the *PDGFRA* D842V mutation are insensitive to current TKI therapies; once these patients progress to unresectable or metastatic disease (the population of interest for this submission), they have a significantly worse prognosis. Therefore, in the absence of any other effective therapy option, and in line with NICE-approved treatment options, clinical experts from England and Wales stated that they would always inform their patients that the available TKIs have a very low probability of being effective for patients with their mutational status and that they may experience adverse effects, but still give them the option of receiving treatment as per standard practice.[5] In a survey of clinical experts, the majority of participants confirmed that, excluding patients who receive experimental therapies via clinical trials, compassionate use programmes or other means, patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in England and Wales are treated with imatinib, sunitinib and regorafenib, with most indicating that these would be used as first-, second- and third-line therapies, respectively, despite the lack of efficacy of these treatments.[1]

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.

The current treatment pathway for patients with *PDGFRA* D842V-mutated GIST, based on the available evidence, is presented in Figure 1.

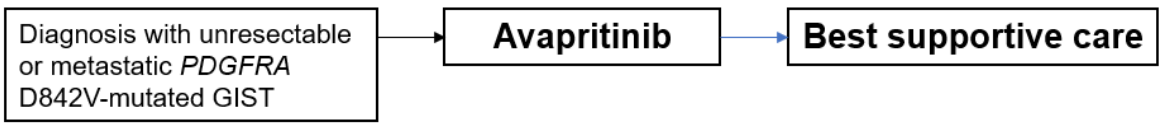
Figure 1: Current clinical pathway for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation



Key: GIST, gastrointestinal stromal tumour; *PDGFRA*, platelet-derived growth factor receptor alpha.
Source: Clinical survey conducted by Blueprint Medicines.[1]

Clinicians agreed that the majority of patients in England and Wales would receive mutational testing before, during, or as an immediate response to diagnosis with unresectable or metastatic GIST.[1] Following the introduction of avapritinib for patients with the *PDGFRA* D842V mutation, clinical experts from England and Wales confirmed that they would follow the treatment pathway presented in Figure 2.[1] As these patients would now have an effective treatment option available to them, they would no longer need to consider using the currently available TKIs and so would only use avapritinib, followed by best supportive care.

Figure 2: Proposed future clinical pathway for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation following the introduction of avapritinib



Key: GIST, gastrointestinal stromal tumour; *PDGFRA*, platelet-derived growth factor receptor alpha.
Source: Clinical survey conducted by Blueprint Medicines[1]

B.1.3.4. Epidemiology

GISTs are a rare form of cancer, and avapritinib was granted orphan designation by the EMA in this population.[3] Only a small proportion of patients progress to unresectable or metastatic disease, and only 5–6% of those patients have a *PDGFRA* mutation in exon 18 (including D842V).[13, 14] However, there are limited data available on the specific incidence and prevalence of GISTs. ESMO and the BSG use European studies to estimate an unadjusted incidence of between 1 and 1.5/100,000/year.[11, 39] The BSG guideline on GIST[6] also uses data from the Rhône-Alpes region of France[40] and personal communication from the National Health Service (NHS) England Cancer Registry to suggest an incidence of just under 11 patients per million per annum, equating to 650 clinically meaningful new cases a year in the UK and approximately 900 in total. The BSG states that accurate data on prevalence in the UK are not yet available.[6] A UK epidemiological model developed by Starczewska and colleagues estimated that the prevalence and absolute number of patients with unresectable or metastatic GIST was below the ultra-orphan disease threshold of 2/100,000 population used in England and Wales for first-, second- and third-line treatment.[41] Their focus was on calculating third-line patients with an estimated prevalence of 1/100,000 and a prevalence count of 598.[41]

Using figures from the literature and expert clinical opinion, it is estimated that there are 30–40 patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation in England and Wales, with approximately five new patients diagnosed per year.[1] Therefore, it is clear that this population meets the criteria as an ultra-orphan condition.

B.1.3.5. Summary of the limitations of current clinical practice and the unmet need for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST

There are currently no effective treatment options available for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation. Current TKIs are known to have extremely limited efficacy for these patients, providing an expected overall response rate (ORR) of 0%, median progression-free survival (PFS) of only 3–5 months and median OS of 13–15 months.[15-17]

Current TKIs are also all associated with high levels of adverse events (AEs), with most, if not all, patients experiencing at least one mild or moderate event.[42-45] In the pivotal clinical trial used to support the imatinib NICE submission, 97.3% of imatinib-treated GIST patients experienced AEs of any grade, with 52.4% experiencing Grade ≥ 3 events.[29, 42] For the sunitinib NICE submission, 94% of GIST patients treated with sunitinib experienced AEs of any grade, with 35% experiencing serious AEs (Grade ≥ 3 events were not reported).[44] For the regorafenib NICE submission, 100% of GIST patients treated with regorafenib experienced AEs of any grade, with 61.4% experiencing Grade ≥ 3 events and 28.8% experiencing serious events.[45] As discussed in Section B.1.3.3, patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST are treated with imatinib, sunitinib and regorafenib in England and Wales despite the lack of efficacy. Therefore, while the AEs described above are counterbalanced by positive treatment outcomes for patients without the *PDGFRA* D842V mutation, patients with the *PDGFRA* D842V mutation will experience these AEs without the benefits associated with responding to treatment, including higher PFS and OS. These patients will be experiencing the high symptom burden associated with their unresectable or metastatic disease and related negative impacts on HRQL, as described previously in Section B.1.3, in addition to further disutility associated with AEs related to treatment with established clinical management.

Patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST are effectively given a choice between a) burdensome, ineffective treatment with current TKIs as part of established clinical management, b) best supportive care, or c) enrolment on an appropriate clinical trial, if one is available. Therefore, there is a clear, significant unmet need for an effective, targeted treatment option for these patients that both improves their quality of life by reducing the burden of their disease and substantially increases their life expectancy to match or surpass that of GIST patients with other mutations.

B.1.4. Equality considerations

We do not expect any equality issues to arise with the use of avapritinib.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

- In appendix D describe the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.
- See section 2.1 of the user guide for full details of the information required in appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The pivotal regulatory evidence to support avapritinib for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation comprises the ongoing Phase I, including a dose escalation and a dose expansion phase, single-arm, open label, multicentre clinical trial (including one site in the UK); the NAVIGATOR study, which is the focus of this submission. The primary sources of evidence for this study presented throughout this submission are:

- An internal analysis of the January 2020 data cut for the NAVIGATOR study (median follow up: [redacted] months)[46]
- The NAVIGATOR study clinical study report (CSR), for the November 2018 data cut[47] (median follow up [redacted] months)

A summary of the NAVIGATOR study is presented in Table 4.

Table 4: Clinical effectiveness evidence

Study	NAVIGATOR; BLU-285-1101				
Study design	Phase I, including a dose escalation and a dose expansion phase, open-label, single-arm, multicentre study				
Population	Adult patients with unresectable or metastatic GIST				
Intervention(s)	Avapritinib				
Comparator(s)	Not applicable				
Indicate if trial supports application for marketing authorization	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	

Rationale for use/non-use in the model	The NAVIGATOR study presents the pivotal regulatory, clinical evidence in support of avapritinib in the population directly relevant to the decision problem.
Reported outcomes specified in the decision problem	The outcome measures specified in the decision problem are: • **Overall survival** • Response rate (including partial response rate and duration of response) • **Progression-free survival** • **Adverse effects of treatment**
All other reported outcomes	• Time to response • **Time on treatment** • Radiographic tumour reductions
Key: GIST, gastrointestinal stromal tumour. **Notes:** Outcomes presented in bold are those used in the economic model.	

Part I of the NAVIGATOR study was a dose-escalation study to determine the maximum tolerated dose or the recommended dose of avapritinib, while Part II of the NAVIGATOR study was an expansion study to determine the safety and efficacy of avapritinib at the selected dose. In Part II of the study, patients were initially started at a dose of 400 mg once daily, which was reduced to 300 mg once daily based on emerging safety data. The following doses were used for the 56 patients with *PDGFRA* D842V-mutated disease in the NAVIGATOR study:

- [redacted] patients were treated at a dose < 300 mg once daily (including starting doses of 30 mg, 60 mg, 90 mg, 135 mg and 200 mg)
- [redacted] patients were treated at a dose of 300 mg once daily
- [redacted] were treated at a dose of 400 mg once daily
- [redacted] patient was treated at a dose of 600 mg

No differences in efficacy outcomes were evident between the 300 mg and 400 mg dose groups (see Appendix L); therefore, these groups were analysed together to provide the evidence for the MAA submission to the EMA. Subsequently, when the efficacy outcomes were compared across all doses, there were also no significant differences in results. Therefore, in order to provide the maximum amount of data to inform the economic model for this ultra-orphan population, the 'all dose' group was selected as being the most appropriate source of evidence. As the primary source of data used in the economic model, the results for the 'all dose' group are presented in

Section B.2.6. Additional results from each of the individual dose groups are presented separately in Appendix L.

The primary data cut for the NAVIGATOR study was from November 2018 (median follow up: [redacted] months); this is the data cut for which the majority of data were available. A more recent data cut became available in January 2020 (median follow up: [redacted] months), providing updated evidence for OS, PFS and time on treatment (ToT). The most recent data are used in the model and presented as the primary source of evidence, where available. For ease of reference, Table 5 presents a summary of the treatment outcomes from the NAVIGATOR study, including the data cut that was used and a link to where the evidence is presented within the submission document.

Table 5: Treatment outcomes in the NAVIGATOR study

Outcome	Data cut	Location in submission
Overall survival		
'All dose' group	January 2020	Section B.2.6
Other dose groups	November 2018	Appendix L.2
Progression-free survival		
'All dose' group	January 2020	Section B.2.6
Other dose groups	November 2018	Appendix L.3
Response		
'All dose' group	November 2018	Section B.2.6
Other dose groups	November 2018	Appendix L.4
Duration of response		
'All dose' group	November 2018	Section B.2.6
Other dose groups	November 2018	Appendix L.5
Time to response		
'All dose' group	November 2018	Section B.2.6
Other dose groups	November 2018	Appendix L.6
Radiographic tumour reductions		
'All dose' group	November 2018	Section B.2.6
Other dose groups	November 2018	Appendix L.7
Time on treatment		
'All dose' group	January 2020; November 2018	Section B.2.10
Other dose groups	November 2018	Section B.2.10

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. The NAVIGATOR study

A summary of the methodology used in the NAVIGATOR study is presented in Table 6. This study was a Phase I, including a dose escalation and a dose expansion phase, single-arm, open label, multicentre clinical trial (including one site in the UK) to evaluate the efficacy and safety of avapritinib in patients with unresectable or metastatic GIST. The study population was divided into three groups; the group of patients relevant to this submission is the group of patients with the *PDGFRA* D842V mutation (Group 2).

Table 6: Summary of the trial methodology for the NAVIGATOR study

Trial number (acronym)	NCT02508532 (NAVIGATOR; BLU-285-1101)
Location	The NAVIGATOR study was conducted at 19 centres; eight in the US, eight in Europe (Belgium, France, Germany, Italy, Netherlands, Poland, Spain and the UK) and one in Asia (Republic of Korea).
Trial design	The NAVIGATOR study was a Phase I, including a dose escalation and a dose expansion phase, open-label, single-arm, multicentre 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 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) • 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)

Eligibility criteria for participants	**Inclusion criteria** Patients were eligible for inclusion in the study if they met the following criteria: • Age ≥ 18 years • For Part 2: – Group 2: Patients must have had a confirmed diagnosis of unresectable GIST with a D842V mutation in *PDGFRA*. The *PDGFRA* mutation should have been identified by local or central assessment, either in an archival tissue sample or a new tumour biopsy obtained prior to treatment with avapritinib – At least one measurable lesion defined by the mRECIST Version 1.1 for patients with GIST – A tumour sample (archival tissue or a new tumour biopsy) had been submitted for mutational testing • ECOG performance status of 0–2 • Patient or legal guardian, if permitted by local regulatory authorities, provided informed consent to participate in the study **Exclusion criteria** Patients were excluded from the study if they met any of the following criteria: • Patient had any of the following within 14 days prior to the first dose of study drug: – Alanine aminotransferase and aspartate aminotransferase >3 × ULN if no hepatic metastases were present; > 5 × ULN if hepatic metastases were 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 – Platelet count < 90 × 109/L – Absolute neutrophil count < 1.0×109/L – Haemoglobin < 9 g/dL. Transfusion and erythropoietin may have been used to reach at least 9 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug • Patient received an anticancer drug less than five half-lives or 14 days (whichever was shorter) prior to the first dose of study drug • Patient had received neutrophil growth factor support within 14 days of the first dose of study drug • Patient required therapy with a concomitant medication that was a strong inhibitor or strong inducer of cytochrome P450 (CYP) 3A4 • Patient had a major surgical procedure (minor surgical procedures such as central venous catheter placement, tumour needle biopsy, and feeding tube placement were not considered major surgical procedures) within 14 days of the first dose of study drug • Patient had a history of another primary malignancy that had been diagnosed or required therapy within 1 year prior to the first dose of study drug. The following were exempt from the 1-year limit:

	completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer and completely resected carcinoma in situ of any site • Patient had a QT interval corrected using Fridericia's formula (QTcF) > 450 ms • Patient had a history of a seizure disorder (e.g. epilepsy) or requirement for anti-seizure medication • Patient had a history of a cerebrovascular accident or transient ischaemic attacks within 1 year prior to the first dose of study drug • Patient had a known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding • Patient had a primary brain malignancy or metastases to the brain • Patient had clinically significant uncontrolled cardiovascular disease, including congestive heart failure Grades II, III or IV according to the New York Heart Association classification, myocardial infarction or unstable angina within the previous 6 months, or poorly controlled hypertension • Patient had a known diagnosis of human immunodeficiency virus infection or active viral hepatitis; viral testing was not required • Patient was unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests or other study procedures, and study restrictions • Women who were unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 30 days after the last dose of study drug • Pregnant women as documented by a serum β-hCG pregnancy test consistent with pregnancy obtained within 7 days prior to the first dose of study drug. Women with β-hCG values that were within the range for pregnancy but were not pregnant (false-positives) may have been enrolled with written consent of the sponsor after pregnancy had been excluded. Women of non-childbearing potential (postmenopausal, hysterectomy, bilateral salpingectomy or bilateral oophorectomy) did not require a serum β-hCG pregnancy test • Women who were breast feeding • Patient had a prior or ongoing clinically significant illness, medical condition, surgical history, physical finding or laboratory abnormality that, in the Investigator's opinion, could have affected the safety of the patient, altered the absorption, distribution, metabolism or excretion of the study drug, or impaired the assessment of study results
Settings and locations where the data were collected	• Patients were to present to the study centre on Cycle 1 Day 1 for the first dose of study drug and serial PK sampling, pharmacodynamic sample collection, vital signs measurement, ECG monitoring, safety monitoring and AE recording. Approximately 20 patients in Groups 1 and 2 at selected sites were to participate in continuous ECG monitoring for extraction of ECGs at the times of PK sampling; Holter recordings were to be collected in Cycle 1 on Days 1, 2, and 15.

	• During Cycle 1, patients were to attend study centre visits on Days 1, 2 and 15. On Day 15, patients were to undergo simplified safety monitoring and dense PK sampling • During Cycle 2, all patients were to attend study centre visits on Day 1 only for safety monitoring and PK blood draws. • After Cycle 2, patients were to return to the study centre on Day 1 of each subsequent cycle through to Cycle 13 for safety monitoring and (through Cycle 4, Day 1) PK blood draws. • After Cycle 2 (Cycle 3, Day 1) and every 2 cycles thereafter, patient's tumour status was to be assessed by CT or MRI through to Cycle 13. • After completion of 13 cycles, patients were to attend study centre visits every 3 cycles on Day 1 for safety monitoring and a tumour status assessment (e.g., Cycle 16, Day 1; Cycle 19, Day 1, etc) • Patients could continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, PD, death or closure of the study by the sponsor • All patients were to attend an end of treatment visit within 14 (± 7) days after the last dose of study drug. • A safety follow-up telephone contact for resolution of any residual AEs was to be made on Day 30 (+ 7 days) after the last dose of study drug, or at the time the patient initiated another antineoplastic therapy. Thereafter, patients were to be followed for disease assessment, subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent or closure of the study by the sponsor.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	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 (these were the patients that were included in the analyses for the economic model): • [redacted] patients were treated at a dose < 300 mg QD (including starting doses of 30 mg, 60 mg, 90 mg, 135 mg and 200 mg) • [redacted] patients were treated at a dose of 300 mg QD • [redacted] were treated at a dose of 400 mg QD • [redacted] patient was treated at a dose of 600 mg Because of similarity in response to avapritinib across the 300 mg and 400 mg groups, and because most patients who started at 400 mg had dose reductions to 300 mg, data from these starting dose groups were pooled and presented as the 300/400 mg group. Given the ultra-orphan nature of the disease, the similarity in outcomes between dose groups and in order to maximize the data available, data for the 'all dose group' were used as the primary source of

	evidence. However, data are presented separately by dose in Appendix L, where available. If a patient forgot to take their morning dose, he/she was to take avapritinib by 4:00 PM that day. If the dose was not taken by 4:00 PM, that dose was to be omitted and the patient was to resume treatment with the next scheduled dose the following morning. If a patient vomited during or after taking avapritinib, re-dosing was not permitted until the next scheduled dose. A temporary discontinuation (up to 2 weeks) in avapritinib dosing was allowed for patients who required an interruption (e.g. for surgery or other procedure) during the treatment period. Avapritinib was to be discontinued 48 hours before the procedure and resumed 48 hours after the procedure was completed. **Permitted concomitant therapy** Medications and treatments other than those specified below, including palliative and supportive care for disease-related symptoms, were permitted during the study. Patients were to be closely monitored and treatment was to be instituted for disease-related symptoms as appropriate. Supportive care measures for treating AEs were to be instituted as soon as they were recognized. Antiemetic treatments may have been used at the Investigator's discretion and in accordance with the ASCO guidelines or equivalent after documented nausea or vomiting had occurred without medications having been used. The choice of antiemetic treatment, if required, was to be made at the Investigator's discretion. During Part 2 of the study, prophylaxis for nausea and vomiting may have been instituted at the investigator's discretion. Anti-diarrhoea medications may also have been used at the Investigator's discretion. **Prohibited concomitant therapy** • Medications that are strong CYP3A4 inhibitors or strong CYP3A4 inducers • Any investigational agent or device other than avapritinib • Any antineoplastic agent other than avapritinib • Neutrophil growth factor support was prohibited within 14 days prior to the first dose of study drug and throughout Cycle 1, unless the patient experienced a DLT of neutropenia Radiation therapy to target lesions or surgical removal of target lesions was considered indicative of PD **Concomitant therapy to be used with caution** • Medications that are CYP2C9, CYP3A4, or breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index • Medications that are known to increase the risk of seizures In addition, other antacids were to be taken at a timepoint that was not proximal to study drug administration (at least 3–4 hours before or after study drug administration).

Primary outcomes (including scoring methods and timings of assessments)	• ORR, defined as the rate of centrally confirmed CR or PR by mRECIST Version 1.1 • Overall safety profile of avapritinib, as assessed by the type, frequency, severity, timing and relationship to study drug of any AEs, SAEs and changes in vital signs, ECGs and safety laboratory tests
Other outcomes used in the economic model/specified in the scope	• DoR, as per mRECIST Version 1.1 • PFS, as per mRECIST Version 1.1 • CBR, as per mRECIST Version 1.1 • OS • Time to response was not specified in the protocol as an exploratory endpoint but was included in the statistical analysis plan (SAP) as it was considered to be helpful in the interpretation of study results
Pre-planned subgroups	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 November 2018 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) Corresponding forest plots were provided based on the odds ratio or hazard ratio for each subgroup.
Key: ASCO, American Society of Clinical Oncology; AE, adverse event; BCRP, breast cancer resistance protein; CBR, clinical benefit rate; cm, centimetre; CR, complete response; DLT, dose limiting toxicity; DoR, duration of response; ECG, electrocardiogram; GIST, gastrointestinal stromal tumour; PK, pharmacokinetic; mg, milligram; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; QD, once daily; SAE, serious adverse event; UK, United Kingdom; US, United States. **Source:** NAVIGATOR CSR.[47]	

B.2.3.2. Baseline characteristics

As described in Section B.2.2, the focus of this submission is the 56 patients treated with avapritinib in the NAVIGATOR study at any dose. Details on the participant flow are presented in Appendix D.2.

The baseline characteristics for the 56 'all dose' patients with the *PDGFRA* D842V mutation in the NAVIGATOR study are presented in Table 7 (baseline characteristics

for the other dose groups are presented in Appendix L.1). Patients had a median age of [redacted] ([redacted]% were 65 or over) and were predominantly male ([redacted]%) and white ([redacted]%), with [redacted]% of patients being from Europe. It is important to note that the patients included in the NAVIGATOR study were at an advanced disease stage at baseline, with [redacted]% of the population having unresectable GIST and [redacted]% having metastatic disease. In total, [redacted]% of patients had received prior treatment with imatinib (first line), [redacted]% had received prior treatment with sunitinib (second line) and [redacted]% had received prior treatment with regorafenib (third line). [redacted] patients ([redacted]%) had not received any prior TKI therapy and were therefore being treated with avapritinib as a first-line therapy.

UK clinical experts agreed that the population of patients seen in the NAVIGATOR study was reflective of the unresectable or metastatic *PDGFRA* D842V-mutated GIST population that they would see in clinical practice in England and Wales.[1] This is further supported by the fact that [redacted] out of the 56 patients with the *PDGFRA* D842V mutation ([redacted]%) were from the UK, which is a large proportion for an international study.

Table 7: Baseline characteristics for patients with the *PDGFRA* D842V mutation in the NAVIGATOR study

Baseline characteristics	Avapritinib; all doses[a] N = 56
Age, mean (standard deviation)	[redacted]
Age, median (range)	[redacted]
Age ≥ 65, n (%)	[redacted]
Sex, male, n (%)	[redacted]
Ethnicity, n (%)	
• Hispanic or Latino	[redacted]
• Not Hispanic or Latino	[redacted]
• Not reported	[redacted]
• Unknown	[redacted]
Race, n (%)	
• Asian	[redacted]
• Black or African American	[redacted]
• White	[redacted]
• Unknown	[redacted]
• Other	[redacted]

Baseline characteristics	Avapritinib; all doses[a] N = 56
Race group, n (%)	
• White	[redacted]
• Non-white	[redacted]
• Unknown	[redacted]
Region, n (%)	
• US	[redacted]
• Europe	[redacted]
• Asia	[redacted]
Height, cm, mean (standard deviation); median (range)	[redacted]
Weight, kg, mean (standard deviation); median (range)	[redacted]
BMI, kg/m^2, mean (standard deviation); median (range)	[redacted]
ECOG performance status, n (%)	
• 0	[redacted]
• 1	[redacted]
• 2	[redacted]
Largest target lesion size by central radiographic assessment, n (%)	
• ≤ 5 cm	[redacted]
• > 5 to ≤ 10 cm	[redacted]
• > 10 cm	[redacted]
Largest target lesion size by central radiographic assessment, n (%)	
• ≤ 10 cm	[redacted]
• > 10 cm	[redacted]
Patient staged at screening by TNM, n (%)	
• Yes	[redacted]
• No	[redacted]
• Unknown	[redacted]
Current stage at screening visit by TNM, n (%)	
• Stage III	[redacted]
• Stage IV	[redacted]
• Unknown	[redacted]
Patients with metastatic disease, n (%)	
• Yes	[redacted]
• No	[redacted]
Primary tumour site of GIST at diagnosis, n (%)	
• Stomach	[redacted]
• Duodenum	[redacted]

Baseline characteristics	Avapritinib; all doses[a] N = 56
• Jejunum or Ileum	[redacted]
• Rectum	[redacted]
• Omentum	[redacted]
• Colon	[redacted]
• Peritoneum	[redacted]
Site of metastatic disease, n (%)	
• Abdomen/viscera	[redacted]
• Adrenals	[redacted]
• Bone	[redacted]
• Colorectal	[redacted]
• Liver	[redacted]
• Lymph nodes	[redacted]
• Lung	[redacted]
• Pancreas	[redacted]
• Peritoneum	[redacted]
• Pleura	[redacted]
• Other	[redacted]
Prior surgical resection, n (%)	
• Yes	[redacted]
• No	[redacted]
Type of resection, n (%)	
• Total	[redacted]
• Partial	[redacted]
• Other	[redacted]
Prior imatinib, n (%)	
• Yes	[redacted]
• No	[redacted]
Prior sunitinib, n (%)	
• Yes	[redacted]
• No	[redacted]
Prior regorafenib, n (%)	
• Yes	[redacted]
• No	[redacted]

Key: BMI, body mass index; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; *PDGFRA*, platelet-derived growth factor receptor alpha; QD, once daily; TNM, Tumour, Node, Metastasis.
Notes: [a], includes patients with < 300 mg QD and 600 mg QD starting dose.
Source: NAVIGATOR CSR; Table 14.1.4.1.2.

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

In appendix D, provide details of the numbers of participants eligible to enter the trials.

Table 8 presents a summary of the statistical analyses used in the NAVIGATOR study.

Table 8: Summary of statistical analyses

Trial number (acronym)	NCT02508532 (NAVIGATOR; BLU-285-1101)
Hypothesis objective	The hypothesis was that the ORR for patients with the *PDGFRA* D842V mutation treated with avapritinib was significantly greater than 10%
Statistical analysis	**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.[48] The censoring rules based on the EMA guidelines were used as a sensitivity analysis.[49]

	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.[50] 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.[50] 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. **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.[50] 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.
Sample size, power calculation	In Part 2 Group 2, a sample size of 31 patients with the *PDGFRA* D842V mutation was expected to allow testing of the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 35% using exact binomial test, with 90% power assuming a two-sided Type 1 error rate of 0.05. An observed ORR of ≥ 26% in 31 patients would result in an exact binomial 95% CI with a lower bound greater than 10%, which was clinically meaningful, and exceeded the ORR expected with available therapies.[15, 16] The target was to enrol up to 35 patients with the *PDGFRA* D842V mutation.
Data management, patient withdrawals	Patients could continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, PD, death or closure of the study by the sponsor. All patients were to attend an end-of-treatment visit within 14 (± 7) days after the last dose of study drug. A safety follow-up telephone contact for resolution of any residual AE was to be made on Day 30 (+ 7 days) after the last dose of study drug, or at the time the patient initiated another antineoplastic therapy. Thereafter, patients were to be followed for disease assessment, subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent, or closure of the study by the sponsor.
Key: AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CSR, clinical study report; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, US Food and Drug Administration; KM, Kaplan–Meier; mRECIST, modified Response Evaluation Criteria in Solid Tumours; NE, not evaluated; ORR, overall response rate; OS, overall survival; PD, progressive disease; *PDGFRA*, platelet-derived growth factor receptor alpha; PFS, progression-free survival; PR, partial response; SD, stable disease. **Source:** NAVIGATOR CSR.	

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

In appendix D, provide the complete quality assessment for each trial.

The NAVIGATOR study was considered to be a high-quality study and was conducted according to Good Clinical Practice. See Appendix D.3 for full details of the quality assessment for the NAVIGATOR study using the Downs and Black checklist,[51] which is recommended for use in non-randomized controlled trial (non-RCT) and observational studies.

B.2.6. Clinical effectiveness results of the relevant trials

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 anticipated to be 300 mg once daily; however, analysis of the data for the different dose groups showed no significant difference in results for any starting dose. Given the lack of dose dependency across the range of doses used, and in order to provide the maximum amount of patient data for this ultra-orphan population, the evidence for the combined 'all dose' group was considered to be the primary source of evidence from the NAVIGATOR study. These are the data used to inform the economic model presented in Section B.3.

The data for the other dose groups are presented in Appendix L.

B.2.6.1. Overall survival (January 2020 data cut)

Table 9 presents the OS data, from the January 2020 data cut, for patients treated with avapritinib in the NAVIGATOR study. With a median follow-up of [redacted] months, median survival was [redacted]. At 42 months, [redacted]% of patients were still alive. The Kaplan–Meier curve for OS is presented in Figure 3.

[redacted] of the eight UK patients ([redacted]%) included in the study were still alive at the time of the January 2020 data cut, with a median follow-up of [redacted] months.

Table 9: Overall survival (patients with the *PDGFRA* D842V mutation; January 2020 data cut)

Overall survival	Avapritinib; all doses[b] (N = 56)
Kaplan–Meier estimates[e]	
• Median, months (95% CI)	[redacted]
• 6 months, %	[redacted]
• 12 months, %	[redacted]
• 18 months, %	[redacted]
• 24 months, %	[redacted]
• 30 months, %	[redacted]
• 36 months, %	[redacted]
• 42 months, %	[redacted]

Key: CI, confidence interval; *PDGFRA*, platelet-derived growth factor receptor alpha.
Notes: Overall survival 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], includes patients who received a starting dose of either 300 mg or 400 mg of avapritinib; [b], including patients with a starting daily dose of 600 mg and < 300 mg; [c], Kaplan–Meier estimate with censoring at date of death; [d], median survival time for patients that did not die during the study; [e], Kaplan–Meier estimates with censoring at the earlier of the data cut-off date and the last date known alive + 1.
Source: The NAVIGATOR study; analysis of January 2020 data cut.[46]

Figure 3: Kaplan–Meier curves of overall survival (patients with the *PDGFRA* D842V mutation; January 2020 data cut)

Key: *PDGFRA*, platelet-derived growth factor receptor alpha.
Source: The NAVIGATOR study; analysis of January 2020 data cut.[46]

B.2.6.2. Progression-free survival (January 2020 data cut)

Table 10 presents the PFS data, from the January 2020 data cut, for patients treated with avapritinib in the NAVIGATOR study. Median PFS was [redacted] months, with [redacted]% of patients still alive and progression free at 42 months. As the data from this study are not fully mature, the median PFS should be interpreted with caution. The Kaplan–Meier curve for PFS is presented in Figure 4.

Table 10: Summary of progression-free survival (patients with the *PDGFRA* D842V mutation; January 2020 data cut)

Progression-free survival	Avapritinib; all doses[a] (N = 56)
Kaplan–Meier estimates, %	
• Median, months (95% CI)	[redacted]
• 6 months, %	[redacted]
• 12 months, %	[redacted]
• 18 months, %	[redacted]
• 24 months, %	[redacted]
• 30 months, %	[redacted]
• 36 months, %	[redacted]
• 42 months	[redacted]

Key: CI, confidence interval; *PDGFRA*, platelet-derived growth factor receptor alpha.
Notes: Progression-free survival 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, progression-free survival is censored at the date of last valid assessment that is stable or better. The table presents number and percentage of *PDGFRA* D842V patients (n [%]). CIs are calculated using the linear transformation.
[a], including patients with a starting daily dose of < 300 mg, 300 mg, 400 mg and 600 mg
Source: The NAVIGATOR study; analysis of January 2020 data cut.[46]

Figure 4: Kaplan–Meier curves of progression-free survival (patients with the *PDGFRA* D842V mutation; January 2020 data cut)

Key: *PDGFRA*, platelet-derived growth factor receptor alpha.
Source: The NAVIGATOR study; analysis of January 2020 data-cut.

B.2.6.3. Overall response rate (November 2018 data cut)

Table 11 presents the response rates from the NAVIGATOR study. Patients with the *PDGFRA* D842V mutation treated with any dose of avapritinib had an ORR of [redacted]%. This included:

- [redacted] complete responses (CRs) ([redacted]%)
- [redacted] partial responses (PRs) ([redacted]%)

Results were similar across doses, with an ORR of [redacted]% in the licensed 300 mg dose. Further details of the results for other doses are presented in Appendix L.4.

The clinical benefit rate (CBR), defined as the proportion of patients with confirmed CR/PR or stable disease (SD) lasting four or more cycles from first dose date, and

the disease control rate (DCR), defined as the proportion of patients whose best response was CR, PR or SD, are extremely important outcomes for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST. Given the lack of alternative effective treatment options, avoiding progressive disease for longer 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 [redacted]%, showing that no patients went straight to progressive disease. The CBR was [redacted]%, with only [redacted] patients not experiencing CR, PR or SD for four or more cycles from the date of the first dose.

Table 11: Summary of best response[a] (patients with the *PDGFRA* D842V mutation; November 2018 data cut)

Response rates	Avapritinib; all doses[b] (N = 56)
ORR[d], n (%)	[redacted]
• 95% CI[e]	[redacted]
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
CBR[f], n (%)	[redacted]
• 95% CI[e]	[redacted]
DCR, n (%)[g]	[redacted]
• 95% CI	[redacted]

Key: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate; mRECIST, modified Response Evaluation Criteria in Solid Tumours; 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], includes patients with < 300 mg and 600 mg doses; [d], the proportion of patients with a confirmed best response of CR or PR; [e], two-side 95% CI based on exact binomial distribution using the Clopper–Pearson method; [f], the proportion of patients with confirmed CR/PR or SD lasting ≥ 4 cycles from first dose date; [g], the proportion of patients with a confirmed best response of CR, PR or SD.
Source: NAVIGATOR CSR; Table 14.2.1.1.2.

B.2.6.4. Duration of response (November 2018 data cut)

Duration of response (DoR) outcomes from the NAVIGATOR study are presented in Table 12. The median DoR was [redacted] months for patients with the *PDGFRA* D842V mutation who were treated with any dose of avapritinib. As the data from this study

are not fully mature, the median DoR should be interpreted with caution. At 24 months of follow-up, [redacted]% of responders in this group were maintaining this response. For the anticipated licensed dose of 300 mg once daily, the median DoR was [redacted]. Additional DoR evidence for the other treatment dose groups is presented in Appendix L.5.

Table 12: Duration of response using European Medicines Agency censoring rules (patients with the *PDGFRA* D842V mutation)

Duration of response	Avapritinib; all doses[a] (N = 49)
Patients with events, n (%)	[redacted]
Patients censored, n (%)	[redacted]
Kaplan–Meier estimates	
• Median (95% CI)	[redacted]
• 25th, 75th percentile	[redacted]
• 3 months (95% CI)	[redacted]
• 6 months (95% CI)	[redacted]
• 9 months (95% CI)	[redacted]
• 12 months (95% CI)	[redacted]
• 18 months (95% CI)	[redacted]
• 24 months (95% CI)	[redacted]

Key: CI, confidence interval; CR, complete response; CSR, clinical study report; NR, not reported; *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 came first. Patients without confirmed CR or PR were excluded from this analysis. Patients who were still in response at time of data cut-off were censored at their last valid assessment. This table presents the number and percentage of responder patients with the *PDGFRA* D842V mutation (n [%]) in the Safety Population. CIs are calculated using the linear transformation. [a], includes patients with < 300 mg and 600 mg starting dose.
Source: NAVIGATOR CSR; Table 14.2.2.2.2.

B.2.6.5. Time to response (November 2018 data cut)

The median time to response for all patients with the *PDGFRA* D842V mutation treated with avapritinib in the NAVIGATOR study was [redacted] days (Table 13).

The results for the other dose groups are presented in Appendix L.6 and were consistent across all doses.

Table 13: Time to response (CR/PR) by central radiology per mRECIST Version 1.1 (patients with the *PDGFRA* D842V mutation; November 2018 data cut)

Time to response	Avapritinib, all doses[a] (N=49)
Time to first response (CR/PR) Median (range), days	[redacted])

Key: CR, complete response; CSR, clinical study report; 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. [a], including patients with a starting daily dose of 600 mg and < 300 mg.
Source: NAVIGATOR CSR; Table 14.2.2.9.2.

B.2.6.6. Radiographic tumour reductions (November 2018 data cut)

Radiographic tumour reductions were observed in [redacted]% of patients with the *PDGFRA* D842V mutation who were treated with avapritinib in the NAVIGATOR study (Figure 5). [redacted] of the patients with 100% reduction in tumour size did not have a CR per central radiology assessment; [redacted] due to an increase in ascites, [redacted] who had no confirmatory scan available and [redacted] due to persistent non-target lesions. The high proportion of patients and the high percentage of reduction in tumour sizes is an extremely positive outcome for patients in this population.

Figure 5: Waterfall plot of sum diameter of target lesions by central radiology (patients with the *PDGFRA* D842V mutation in the 'all dose' group; November 2018 data cut)

Key: CR, complete response; CSR, clinical study report; PD, progressive disease; *PDGFRA*, platelet-derived growth factor receptor alpha; PR, partial response; SD, stable disease.
Notes: Three patients with 100% decrease in target lesion diameter did not have a CR per central radiology assessment – one due to increase in ascites, one due to having no confirmatory scan available, and one due to persistent non-target lesions.
Source: NAVIGATOR CSR.

B.2.7. Subgroup analysis

Provide a summary of the results for the subgroups in appendix E.

The population of interest for this submission is patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, which was a pre-specified subgroup within the NAVIGATOR study. No additional subgroup analyses were performed within this cohort of patients in this study.

B.2.8. Meta-analysis

The NAVIGATOR study is the only source of evidence for avapritinib in the unresectable or metastatic *PDGFRA* D842V-mutated GIST population. Therefore, a meta-analysis of available evidence is not applicable for this appraisal.

B.2.9. Indirect and mixed treatment comparisons

In appendix D include full details of the methodology for the indirect comparison or mixed treatment comparison.

B.2.9.1. Summary of available evidence for comparison

A summary of the relevant studies identified by the clinical systematic literature review is presented in Table 14, including an assessment of their relevance for inclusion in the submission and for use in the economic model.

Most of the studies identified by the clinical systematic literature review (SLR) contained limited information on patient characteristics, particularly around the lack of clarity on whether the populations were strictly unresectable or metastatic (which is a key driver of treatment outcomes), with some studies specifically including patients with localized disease. This makes comparison with these studies impossible, because resectable GIST has a completely different treatment pathway, i.e. 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.

BLU-285-1002, a retrospective observational study of patients with locally advanced, metastatic or recurrent *PDGFRA* D842V-mutated GIST previously treated with a TKI, was designed to serve as a historical control for efficacy studies of avapritinib. As this study was sponsored by Blueprint Medicines, patient-level data were available. An issue with this study was that, by its design, it also included patients with the *PDGFRA* D842V mutation with localized GIST who were treated with TKIs. This means that the first TKI received by patients in BLU-285-1002 was not necessarily to treat unresectable or metastatic disease. It would therefore have been inappropriate to compare outcomes data for avapritinib in the NAVIGATOR study with those for the first TKI in BLU-285-1002, 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 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. Therefore, the most appropriate approach to comparing avapritinib in the NAVIGATOR study with established clinical management (ECM) in BLU-285-1002 was to use data from the first TKI for unresectable or metastatic disease in BLU-285-1002. 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 versus ECM in the patient population with unresectable or metastatic *PDGFRA* D842V-mutated GIST.

The 2012 study by Cassier et al. had a patient population that was similar to that in the NAVIGATOR study. This study also included the largest subgroup of patients with the *PDGFRA* D842V mutation (n = 32) from the identified literature, and these patients were treated as per current UK standard practice. However, no baseline characteristics were reported specific to the *PDGFRA* D842V mutation subgroup, which made it impossible to perform an adjusted indirect comparison (such as a matching-adjusted indirect comparison).

UK clinicians confirmed that in clinical practice, for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, they would provide information to the patients on the likely lack of efficacy and potential adverse events (AEs) of current TKIs, but would still use these treatments if this was the patient's preference. Clinicians agreed that the outcomes reported by Cassier et al. – which are similar to those reported in the weighted BLU-285-1002 analysis – were reflective of what they would expect to see in clinical practice for these patients in NHS England.[1, 5]

The best source of data for the comparison to avapritinib in the NAVIGATOR study is the weighted comparison to BLU-285-1002, and these are the data that are used as the base case in the economic model. To explore uncertainty, the Cassier et al. study was used to present a naïve comparison to the NAVIGATOR study in a scenario analysis (See Appendix P for evaluation of Cassier et al. data for the economic model and Appendix D.1 for presentation of the outcomes of the Cassier et al. study alongside the outcomes of the NAVIGATOR study). As shown in Section B.2.9.3, the results from Cassier et al. were similar to the weighted outcomes from BLU-285-1002.

Table 14: Summary of relevant studies identified by the clinical systematic literature review

Study	Study design; treatment	Rationale for use/exclusion from the economic model
NAVIGATOR; BLU-285-1101 (NCT02508532)	**Open-label, multicentre (Europe, the US, Asia), single-arm observational study of avapritinib in patients with unresectable or metastatic GIST.**	**Pivotal regulatory data for avapritinib including key evidence for the anticipated licensed population of** [redacted]
BLU-285-1002	**Multicentre (US), retrospective observational study (chart review) of patients with locally advanced, metastatic or recurrent *PDGFRA* D842V-mutated GIST diagnosed from 2000–2016, previously treated with a TKI.**	**Patient-level data were available for this study, allowing for a matched comparison to the NAVIGATOR study.**
Cassier et al., 2012	Retrospective observational study (European survey) of patients with advanced *PDGFRA*-mutant GISTs treated with imatinib at first line (and sunitinib at second line).	Patient population similar to that in the NAVIGATOR study for a naïve comparison (97% versus 96% had metastatic disease; median age: 61 versus 64, respectively);

Study	Study design; treatment	Rationale for use/exclusion from the economic model
		includes 32 patients with the *PDGFRA* D842V mutation treated as per current UK standard practice. However, baseline characteristics were not available for the *PDGFRA* D842V population, and data were less recent than that used in BLU-285-1002. This study was considered by clinicians to be the most appropriate publicly available data to be used in a naïve comparison to the NAVIGATOR study, and therefore this was explored as a scenario analysis.
B222 trial	Phase II open-label dose-ranging randomized trial of imatinib in patients with metastatic GIST (analysis focused on patients with *KIT* or *PDGFRA* mutations).	Only response data were available for three patients with the *PDGFRA* D842V mutation and no baseline characteristics were presented for these patients.
Yoo et al., 2016	Retrospective observational study of patients with advanced *PDGFRA*-mutant GISTs treated with imatinib as first line and sunitinib as second-line in the Asan Medical Centre GIST registry, Seoul, Korea, from 2000 to 2012.	Only nine patients with the *PDGFRA* D842V mutation were included from a Korean registry. Limited baseline characteristics are available for comparison with the NAVIGATOR study, but it appears to be a healthier population, with only 56% of the patients from overall population (N = 18) having metastatic disease (versus 96%) and one patient having a localized tumour.
Osuch et al., 2014	Retrospective, observational study of patients with advanced GIST treated with imatinib in the Clinical Registry of GIST, Poland, from 2001 to 2011.	Polish registry study; data only available for eight patients with the *PDGFRA* D842V mutation, and limited baseline data for comparison with the NAVIGATOR study.
Rutkowski et al., 2012	Single-centre (Poland), prospective cohort study of patients with advanced or inoperable GIST treated with sunitinib as second line after imatinib failure, from 2005 to 2011.	Single-centre study in Poland with a focus on second-line treatment; only 12 patients with the *PDGFRA* D842V mutation and limited baseline data for comparison with the NAVIGATOR study.

Key: GIST, gastrointestinal stromal tumour; KIT, v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; *PDGFRA*, platelet-derived growth factor receptor alpha; TKI, tyrosine kinase inhibitor.
Notes: Studies in bold are those used in the economic model.

B.2.9.2. Weighted comparison of BLU-285-1002 to the NAVIGATOR study

The methods used for this analysis are presented in Appendix D.1. 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 D.1.

Table 15 presents the baseline characteristics for the NAVIGATOR study compared with BLU-285-1002 for the key confounding factors (as presented in Appendix D.1.). 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. 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).[52] It is also worth noting that three patients from BLU-285-1002 were excluded in the analysis presented here because they each received only one TKI, which was given for adjuvant treatment of localized disease; it would therefore have been inappropriate to include data for these patients.

Table 15: Baseline characteristics for the NAVIGATOR study and BLU-285-1002 (at time of first TKI for unresectable or metastatic disease) presenting key confounding factors

Factors	Total	Patients' treatment (study)		
		NAVIGATOR N = 56	BLU-285-1002 N = 19	P-value
Sex				[redacted]
• Male	[redacted]	[redacted]	[redacted]	
• Female	[redacted]	[redacted]	[redacted]	
Age				[redacted]
• < 60 years	[redacted]	[redacted]	[redacted]	
• ≥ 60 years	[redacted]	[redacted]	[redacted]	

Factors	Total	Patients' treatment (study)		
		NAVIGATOR N = 56	BLU-285-1002 N = 19	P-value
Race				
• White				
• Non-white				
• Missing				
Anatomical site				
• Gastric (stomach)				
• Small bowel or rectal (any other organ)				
Metastatic disease				
• No				
• Yes				
ECOG performance status				
• 0				
• 1				
• 2+				
• Missing				
Duration of disease				
• < 3 years				
• ≥ 3 years				
Number of total TKI				
• 1				
• 2				
• 3				
• 4+				

Key: ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
Notes: *, p-value was statistically significant (p ≤ 0.05).
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

B.2.9.2.1. Inverse probability weighting

Logistic regression was used to estimate propensity scores, in line with Technical Support Documents (TSDs) 17 and 18. 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 are used to estimate

propensity scores. The following parameters were included in the model specification:

- 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
- 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. The regression results are reported in Table 16, and the individual patient weights are provided in Appendix N.

Table 16: Regression results from the propensity score logistic regression

	Coef.	Std. Err.	z	P>z	95% CI	
gender	[redacted]					
age_dummy						
anatomical_site						
metastatic_disease						
total_tki_dummy						
duration_dummy						
_cons						

Key: CI, confidence interval; Coef., coefficient; Std. Err., standard error.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

B.2.9.2.2. Inverse probability weighting-adjusted overall survival

The proportion of patients alive at 6, 12, 18 and 24 months for patients treated with avapritinib or ECM is reported in Table 17. Figure 6 presents the inverse probability weighting (IPW)-adjusted Kaplan–Meier survival functions for OS in the NAVIGATOR study and BLU-285-1002. The median survival in BLU-285-1002 is [redacted] months; in contrast, median survival is [redacted] in the NAVIGATOR study.

Table 17: IPW-adjusted Kaplan–Meier survival estimates of OS at key timepoints in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Kaplan–Meier survival estimates	NAVIGATOR	BLU-285-1002
Median, months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Key: ECM, established clinical management; IPW, inverse probability weighting; OS, overall survival.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

Figure 6: IPW-adjusted Kaplan–Meier curves for OS in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Key: ECM, established clinical management; IPW, inverse probability weighting; OS, overall survival; TKI, tyrosine kinase inhibitor.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

The comparison between the two IPW-adjusted survival curves was performed using the Cox regression-based test for equality (Table 18) 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 result was significant, so the null hypothesis can be rejected, and we can say that the differences observed between the two survival curves are not due to chance.

Table 18: Cox regression-based test for equality of survival curves (overall survival)

Treatment	Events observed	Events expected	Relative hazard
Other TKIs	[redacted]	[redacted]	[redacted]
Avapritinib	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			

Key: TKI, tyrosine kinase inhibitor.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

B.2.9.2.3. IPW-adjusted progression-free survival

The fraction of patients alive and progression free at 6, 12, 18 and 24 months for patients treated with avapritinib or ECM is reported in Table 19. The IPW-adjusted Kaplan–Meier survival functions for PFS in the NAVIGATOR study and BLU-285-1002 is reported in Figure 7. The median PFS in BLU-285-1002 was [redacted] months; in contrast, median PFS was [redacted] in the NAVIGATOR study.

Table 19: IPW-adjusted Kaplan–Meier survival estimates of PFS at key timepoints in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Kaplan–Meier PFS estimates	NAVIGATOR	BLU-285-1002
Median, months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Key: ECM, established clinical management; IPW, inverse probability weighting; PFS, progression-free survival.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

Figure 7: IPW-adjusted Kaplan–Meier curves for PFS in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Key: ECM, established clinical management; IPW, inverse probability weighting; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

The comparison between the two IPW-adjusted survival curves was performed using the Cox regression-based test for equality (Table 20) 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 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.

Table 20: Cox regression-based test for equality of survival curves (PFS)

Treatment	Events observed	Events expected	Relative hazard
Other TKIs	[redacted]	[redacted]	[redacted]
Avapritinib	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			

Key: PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

B.2.9.3. Uncertainties in the indirect and mixed treatment comparisons

There is some uncertainty in the generalizability of the mix of treatments used in BLU-285-1002 to the treatment pathway used in clinical practice in England and Wales. In clinical practice in England and Wales, most clinicians indicated that imatinib would be used as first-line treatment for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST, with sunitinib and regorafenib used in subsequent lines of therapy.[1] At first line in BLU-285-1002, [redacted]% of patients were treated with imatinib, [redacted]% were treated with sunitinib, [redacted]% were treated with regorafenib and [redacted]% of patients were treated with crenolanib (presented in more detail in Appendix Q). As BLU-285-1002 was based in the US, it is not surprising that there are some differences in the treatments used. 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 treatment pathway for England and Wales confirmed by clinical experts. Furthermore, according to UK clinical experts, existing TKIs are not expected to have any efficacy for patients with the *PDGFRA* D842V mutation,[1] 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 used in BLU-285-1002 may bias these data in favour of the comparator, and the use of these data to reflect UK clinical practice is likely to be conservative.

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. study,[15] which was confirmed by clinicians to be the most appropriate publicly available source of evidence for a naïve comparison to the NAVIGATOR study.[5] Clinicians also agreed that Cassier et al. was reflective of the outcomes they would expect to see for these patients in clinical practice.[1] Figure 8 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 not be expected to 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. Additional evidence from the naïve comparison between the Cassier et al. study and the NAVIGATOR study is presented in Appendix D.1.

Figure 8: Comparison of progression-free and overall survival Kaplan–Meier curves, IPW-adjusted BLU-285-1002 and Cassier et al.

Key: IPW, inverse probability weighting; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study.[17]

B.2.10. Adverse reactions

In appendix F, provide details of any studies that report additional adverse reactions to those reported in the studies in section 2.2.

Data regarding AEs for avapritinib are presented from the entire safety population of the NAVIGATOR study. This included data for patients without the *PDGFRA* D842V mutation, who were treated at fourth line, following failure of imatinib, sunitinib and regorafenib. There is no clinical evidence to suggest that AEs would occur more frequently in patients with or without the *PDGFRA* D842V mutation; 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. This approach aligns with the safety data that were presented to the EMA for the SmPC.

B.2.10.1. Time on treatment for 56 patients in the NAVIGATOR study (January 2020 data cut)

A summary of ToT at the January 2020 data cut in the NAVIGATOR study is presented in Table 21. The median ToT was [redacted] months, with [redacted]% of patients remaining on treatment at 42 months. The Kaplan–Meier curves are presented in Figure 9.

Table 21: Time on treatment for 56 patients in the NAVIGATOR study (January 2020 data cut)

Time on treatment	Avapritinib; all doses[a] (N = 56)
Kaplan–Meier estimates	
Median (95% confidence interval), months	[redacted]
6 months, %	[redacted]
12 months, %	[redacted]
18 months, %	[redacted]
24 months, %	[redacted]
30 months, %	[redacted]
36 months, %	[redacted]
42 months, %	[redacted]
Source: The NAVIGATOR study; analysis of January 2020 data cut.[46]	

Figure 9: Kaplan–Meier curves of time on treatment (56 patients; January 2020 data cut)

Source: The NAVIGATOR study; analysis of January 2020 data cut.[46]

B.2.10.2. Time on treatment and exposure to study drug for *PDGFRA* D842V mutation patients in the NAVIGATOR study (November 2018 data cut)

A summary of the study treatment exposure specific to the patient population with the *PDGFRA* D842V mutation in the NAVIGATOR study is presented in Table 22, providing context to the clinical efficacy evidence presented in Section B.2.6. Patients were treated for a median duration of [redacted] weeks, with a median daily dose of [redacted] mg.

Table 22: Summary of study treatment (patients with the *PDGFRA* D842V mutation; November 2018 data cut)

n (%)	Avapritinib; all doses[a] (N = 56)
Duration of treatment, weeks[b]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Cumulative dose, mg[c]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Average daily dose, mg[d]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Dose intensity, mg/day[e]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Relative dose intensity (%)[f]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Relative dose intensity, n (%)	
• < 75%	[redacted]
• 75% to < 90%	[redacted]
• 90% to < 120%	[redacted]
• 120% to < 150%	[redacted]
• ≥ 150%	[redacted]

Key: CSR, clinical study report; *PDGFRA*, platelet-derived growth factor receptor alpha.
Notes: [a], including patients with a starting daily dose of 600 mg and < 300 mg; [b], duration of treatment is defined as (treatment end date – treatment start date + 1)/7.; [c], cumulative dose (mg) is defined as the sum of all dose actually taken; [d], average daily dose (mg): cumulative dose/number of days actually dosed; [e], dose intensity (mg/days): cumulative dose/treatment duration (days); [f], relative dose intensity: dose intensity/planned dose intensity. Planned dose intensity is based on initial assigned daily dose.
Source: NAVIGATOR CSR; Table 14.1.5.1.2.[47]

B.2.10.3. Time on treatment and exposure to study drug for all patients in the safety population of the NAVIGATOR study (November 2018 data cut)

Across the whole of the NAVIGATOR study, patients were treated for a median duration of [redacted] weeks, with a median daily dose of [redacted]mg. A summary of the study treatment for all patients treated with avapritinib is presented in Table 23. This is

presented to provide context to the safety data, which is presented for the entire NAVIGATOR study to provide the maximum amount of data available for the safety of avapritinib (and therefore also include data for patients without the *PDGFRA* D842V mutation, treated at fourth line, following failure of imatinib, sunitinib and regorafenib).

Table 23: Summary of study treatment (safety population; November 2018 data cut)

n (%)	Avapritinib; all doses[b] (N = 237)
Duration of treatment, weeks[c]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Cumulative dose, mg[d]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Average daily dose, mg[e]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Dose intensity, mg/day[f]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Relative dose intensity (%)[g]	
• Mean (standard deviation)	[redacted]
• Median (range)	[redacted]
Relative dose intensity, n (%)	
• < 75%	[redacted]
• 75% to < 90%	[redacted]
• 90% to < 120%	[redacted]
• 120% to < 150%	[redacted]
• ≥ 150%	[redacted]

Key: CSR, clinical study report.
Notes: a, includes patients who received a starting dose of either 300 mg or 400 mg avapritinib; b, including patients with a starting daily dose of 600 mg and < 300 mg; c, duration of treatment is defined as (treatment end date – treatment start date + 1) / 7.; d, cumulative dose (mg) is defined as the sum of all dose actually taken; e, average daily dose (mg): cumulative dose / number of days actually dosed; f, dose intensity (mg/days): cumulative dose / treatment duration (days); g, relative dose intensity: dose intensity / planned dose intensity. Planned dose intensity is based on initial assigned daily dose.
Source: NAVIGATOR CSR; Table 52[47]

B.2.10.4. Summary of adverse events for all patients in the NAVIGATOR study

Table 24 presents a summary of the AE data for all patients treated with avapritinib at all doses in the NAVIGATOR study. The majority of patients will experience an AE ([redacted]%), with [redacted]% of patients experiencing a Grade ≥ 3 AE and [redacted]% experiencing a serious AE (SAE).

Table 24: Summary of adverse events (safety population; November 2018 data cut)

n (%)	Avapritinib; all doses[b] (N = 237)
Any AE	[redacted]
Any Grade ≥ 3 AE	[redacted]
Any treatment-related AE	[redacted]
Any treatment-related Grade ≥ 3 AE	[redacted]
Any SAE	[redacted]
Any Grade ≥ 3 SAE	[redacted]
Any treatment-related SAE	[redacted]
Patients with AESI of cognitive effects	[redacted]
Patients with AESI of intracranial bleeding	[redacted]
Patients with DLTs	[redacted]
AE leading to discontinuation	[redacted]
AE leading to dose interruption[c]	[redacted]
AE leading to dose reduction	[redacted]
Number of deaths[d]	[redacted]

Key: AE, adverse event; AESI, adverse events of special interest; CSR, clinical study report; DLT, dose-limiting toxicity; SAE, serious adverse event.
Notes: a, includes patients who received a starting dose of either 300 mg or 400 mg avapritinib; b, including patients with a starting daily dose of 600 mg and < 300 mg; c, dose interruptions included doses interrupted due to an AE and missed due to an AE; d, includes deaths that occurred on or after the date of first dose and up to and including the date of last dose + 30 days.
Source: NAVIGATOR CSR; Table 54.[47]

B.2.10.5. Key adverse events for all patients in the NAVIGATOR study

AEs were experienced by [redacted]% of all patients treated with avapritinib at all doses. The most commonly occurring AEs (with incidence ≥ 10%) are presented in Table 25. The most frequent AEs were nausea ([redacted]%) and fatigue ([redacted]%).

Table 25: Adverse events with ≥ 10% incidence (measured in the 300/400 mg dose group) by preferred term and starting dose (safety population; November 2018 data cut)

n (%)	All doses[b] (N = 237)
Patients with ≥ 1 adverse event	[redacted]
Nausea	[redacted]
Fatigue	[redacted]
Anaemia	[redacted]
Periorbital oedema	[redacted]
Vomiting	[redacted]
Decreased appetite	[redacted]
Diarrhoea	[redacted]
Lacrimation increased	[redacted]
Oedema peripheral	[redacted]
Memory impairment	[redacted]
Face oedema	[redacted]
Constipation	[redacted]
Dizziness	[redacted]
Hair colour changes	[redacted]
Blood bilirubin increased	[redacted]
Abdominal pain	[redacted]
Headache	[redacted]
Dyspnoea	[redacted]
Dyspepsia	[redacted]
Hypokalaemia	[redacted]
Dysgeusia	[redacted]
Hypophosphataemia	[redacted]
Aspartate aminotransferase increased	[redacted]
Pyrexia	[redacted]
Alopecia	[redacted]
Insomnia	[redacted]
Weight decreased	[redacted]
Rash	[redacted]
Pleural effusion	[redacted]
Hypomagnesaemia	[redacted]
Cognitive disorder	[redacted]

Key: CSR, clinical study report.
Notes: Adverse events are sorted by decreasing incidence in the 300/400 mg dose group.
a, includes patients who received a starting dose of either 300 mg or 400 mg avapritinib; b, including patients with a starting daily dose of 600 mg (N = 3) and < 300 mg (including starting doses of 30 mg, 60 mg, 90 mg, 135 mg and 200 mg).
Source: NAVIGATOR CSR; Table 55.[47]

B.2.10.6. Grade ≥ 3 adverse events for all patients in the NAVIGATOR study

Grade ≥ 3 AEs were experienced by [redacted]% of all patients treated with avapritinib at all doses. The most commonly occurring Grade ≥ 3 AEs (with incidence ≥ 2%, as measured in the 300/400 mg dose group) are presented in Table 26. The most frequent Grade 3 AE was anaemia ([redacted]%), with the remaining Grade 3 AEs occurring in < 7% of patients.

Table 26: Grade ≥ 3 adverse events with ≥ 2% incidence (measured in the 300/400 mg dose group) by preferred term and starting dose (safety population; November 2018 data cut)

n (%)	Avapritinib; all doses[b] (N = 237)
Patients with ≥ 1 Grade ≥ 3 adverse event	[redacted]
Anaemia	[redacted]
Fatigue	[redacted]
Disease progression	[redacted]
Abdominal pain	[redacted]
Diarrhoea	[redacted]
Hypophosphataemia	[redacted]
Blood bilirubin increased	[redacted]
Neutrophil count decreased	[redacted]
Decreased appetite	[redacted]
General physical health deterioration	[redacted]
Hypokalaemia	[redacted]
Hypertension	[redacted]
Hyponatraemia	[redacted]
Sepsis	[redacted]
Nausea	[redacted]
Dyspnoea	[redacted]
Neutropenia	[redacted]
Ascites	[redacted]
Pleural effusion	[redacted]
Vomiting	[redacted]
Asthenia	[redacted]
Confusional state	[redacted]
Lymphopenia	[redacted]

n (%)	Avapritinib; all doses[b] (N = 237)
Pneumonia	[redacted]

Key: CSR, clinical study report.
Notes: Adverse events are sorted by decreasing incidence in the 300/400 mg dose group.
a, includes patients who received a starting dose of either 300 mg or 400 mg avapritinib; b, including patients with a starting daily dose of 600 mg (N = 3) and < 300 mg (including starting doses of 30mg, 60 mg, 90 mg, 135 mg and 200 mg).
Source: NAVIGATOR CSR; Table 55.[47]

B.2.10.7. Adverse events of special interest

Cognitive effects and cranial bleeding were defined as two AEs of special interest (AESIs) (Table 27). Intracranial bleeding occurred in a small proportion of patients, with only [redacted] patient ([redacted]%) experiencing each of a cerebral haemorrhage, an intracranial haemorrhage and a subdural haematoma. Cognitive effects were experienced by [redacted]% of patients, with [redacted]% experiencing memory impairment, [redacted]% experiencing a cognitive disorder and [redacted]% experiencing a confusional state. Cognitive effects are presented in more detail below.

Table 27: Adverse events of special interest by category and preferred term (safety population; November 2018 data cut)

n (%)	All doses[b] (N = 237)
Cognitive effects	[redacted]
• Memory impairment	[redacted]
• Cognitive disorder	[redacted]
• Confusional state	[redacted]
• Encephalopathy	[redacted]
Intracranial bleeding	[redacted]
• Cerebral haemorrhage	[redacted]
• Haemorrhage intracranial	[redacted]
• Subdural haematoma	[redacted]

Key: CSR, clinical study report.
Notes: Adverse events are sorted by decreasing incidence in the 300/400 mg dose group.
a, includes patients who received a starting dose of either 300 mg or 400 mg avapritinib; b, including patients with a starting daily dose of 600 mg (N = 3) and < 300 mg (including starting doses of 30 mg, 60 mg, 90 mg, 135 mg and 200 mg).
Source: NAVIGATOR CSR; Table 60.[47]

B.2.10.7.1. Post-hoc analysis of cognitive effects

A post-hoc analysis was performed to assess the safety and tolerability of avapritinib at the recommended starting dose of 300 mg, using data from the NAVIGATOR study (November 2018 data cut) and preliminary data from the ongoing VOYAGER RCT: an open-label, Phase III study of avapritinib compared with regorafenib in patients with locally advanced unresectable or metastatic GIST (advanced GIST), previously treated with imatinib and one or two other TKIs (Table 28).[53]

Cognitive effects were experienced by 35% of patients treated with avapritinib at 300 mg once daily in the post-hoc safety analysis: primarily driven by memory impairment (23%). Of these patients, 72% experienced Grade 1 events, which did not affect activities of daily living, and 22% experienced Grade 2 events. Only 6% (n = 4) of these patients experienced Grade 3 events – 2% of the total population – and no patients experienced Grade ≥ 4 events.

Table 28: Cognitive adverse events in post-hoc safety analysis

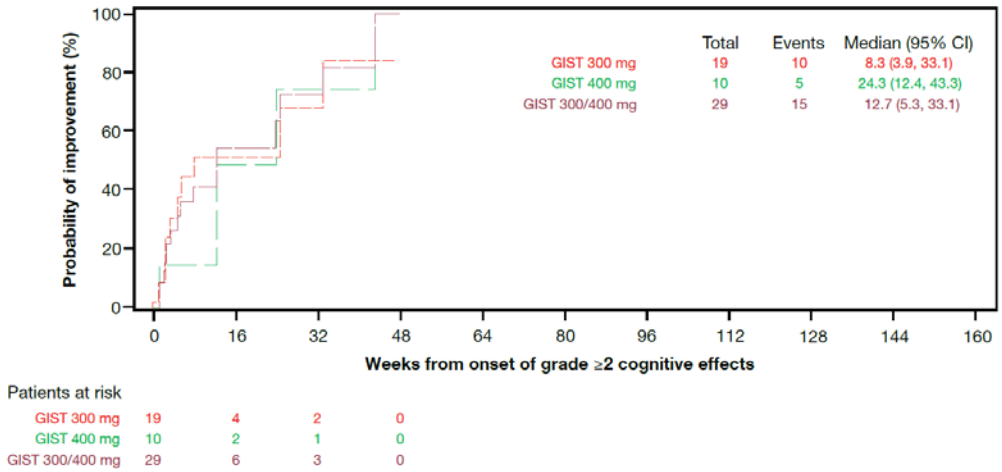
n (%)	Avapritinib 300 mg QD (N = 184)	
	Any grade	**Grade ≥ 3**
Cognitive effects	65 (35)	4 (2)
• Memory impairment	43 (23)	0 (0)
• Cognitive disorder	23 (12)	1 (< 1)
• Confusional state	11 (6)	2 (1)
• Encephalopathy	1 (< 1)	1 (< 1)
Cognitive effects leading to dose interruption	17 (9.2)	
Cognitive effects leading to dose reduction	9 (4.9)	

Key: QD, once daily.
Source: Post-hoc safety analysis of avapritinib 300 mg QD using NAVIGATOR and preliminary VOYAGER data.[53]

As shown in Table 28, for all patients treated with avapritinib at 300 mg once daily, cognitive effects that led to dose interruptions occurred in 9.2% of patients, whereas cognitive effects that led to dose reductions occurred in 4.9% of patients. Across both the 300 mg and 400 mg once daily dose groups, cognitive effects leading to dose interruptions, dose reductions, or both interruptions and reductions occurred in 35% (n = 23), 9% (n = 6), and 15% (n = 10) of patients, respectively. All dose-

modification interventions improved Grade ≥ 2 cognitive effects compared with no action. Median time to improvement to a lower grade was 12.0 days for any intervention versus 32.5 days for no intervention. Symptoms improved fastest with dose interruptions (median 8 days). Figure 10 shows the probability of improvement over time for patients who experienced a cognitive AE.

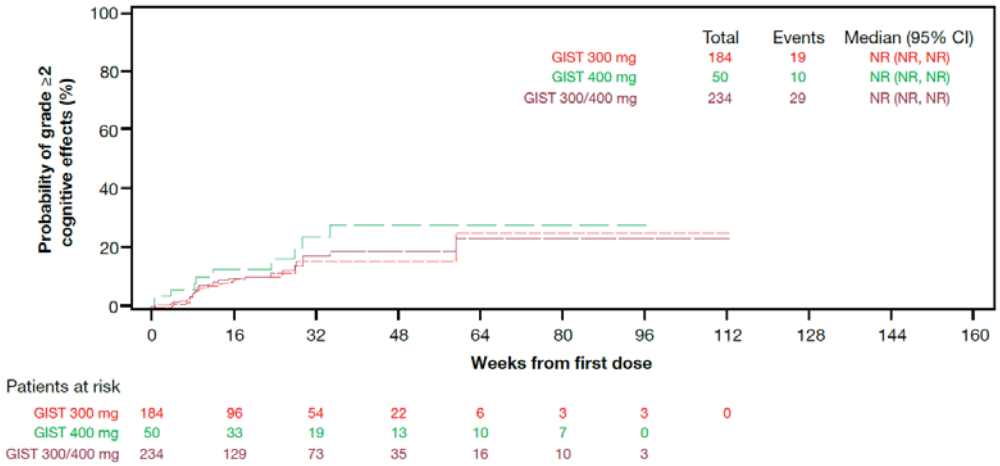
Figure 10: Probability of improvement for patients experiencing a cognitive adverse event



Key: CI, confidence interval; GIST, gastrointestinal stromal tumour.
Source: Post-hoc safety analysis of avapritinib using NAVIGATOR and preliminary VOYAGER data.[53]

Among the 29 patients in the 300/400 mg dose group experiencing a Grade ≥ 2 cognitive effect, 50% had experienced the event by 9 weeks (Figure 11). The rate at which additional patients experience these events after this point decreases over time, up to 7–8 months of treatment. At this point, a plateau is reached; this indicates that if no cognitive AE was experienced by this time, it is unlikely to occur.

Figure 11: Probability of experiencing a cognitive adverse event over time



Key: CI, confidence interval; GIST, gastrointestinal stromal tumour; NR, not reported.
Source: Post-hoc safety analysis of avapritinib using NAVIGATOR and preliminary VOYAGER data.[53]

B.2.10.8. Comparison of adverse events with established clinical management

There is currently no evidence available regarding the AEs experienced by patients undergoing ECM for unresectable or metastatic GIST with the *PDGFRA* D842V mutation. In the absence of these data, evidence from the pivotal clinical trials for these treatments was used for comparison with the NAVIGATOR study.[42-45]

Table 29 presents a comparison of overall AEs between avapritinib and ECM. The current TKIs used as ECM are all associated with high levels of AEs, with most – if not all – patients experiencing at least a mild or moderate event.[42-45] There were some differences in reporting, with incomplete evidence available for the current TKIs. The population in the NAVIGATOR study was also generally a more advanced, sicker patient population. However, the rates of AEs looked broadly similar across the different treatment options, with differences in outcomes being explained by the differences between the patient populations.

Table 29: Adverse events for avapritinib compared to established clinical management

AEs, %	Avapritinib[47] N = 237	Imatinib[29, 42] N = 73	Sunitinib[44] N = 202	Regorafenib[45] N = 132
Any AE	[redacted]	98	94	100

AEs, %	Avapritinib[47] N = 237	Imatinib[29, 42] N = 73	Sunitinib[44] N = 202	Regorafenib[45] N = 132
Treatment-related AE	[redacted]	97.3	83	98.5
Grade ≥ 3 AE	[redacted]	52.4	NR	NR
Treatment-related Grade ≥ 3 AE	[redacted]	NR	NR	61.4
SAE	[redacted]	NR	35	28.8
Treatment-related SAE	[redacted]	NR	20	NR
AE leading to discontinuation	[redacted]	NR	9	6.1
Grade 5 AE	[redacted]	NR	6	15.3

Key: AE, adverse event; CSR, clinical study report; NR, not reported; SAE, serious adverse event.
Source: Avapritinib NAVIGATOR CSR;[47] imatinib;[29, 42] sunitinib;[44] regorafenib.[45]

B.2.10.9. Overview of adverse events

Although AEs occur frequently with avapritinib treatment, the majority of these events can be easily managed with dose modifications and there are clear and robust treatment plans in place to assist clinicians in managing these events. In addition to this, patients treated with avapritinib experience similar levels of adverse events to those experienced by patients treated with established clinical management (Section B.2.10.8).

The key AESIs for avapritinib are cognitive effects, reported by [redacted]% of patients in the NAVIGATOR study. However, in the post-hoc safety analysis using data from the NAVIGATOR study and preliminary data from the ongoing VOYAGER study, these were found to be predominantly Grade 1 events ([redacted]%), which did not affect activities of daily living; [redacted]% of patients experienced Grade 2 events, [redacted]% of patients experienced Grade 3 events ([redacted]% of the analysis population) and [redacted] patients reported a Grade ≥ 4 event. The number of patients experiencing a cognitive effect increases over the first 7 to 8 months of treatment, but the rate of increase slows over time, reaching a plateau where cognitive effect AEs were unlikely to occur if none were experienced by that time. As with overall AEs, there is a robust treatment plan in place for dose interruptions or reductions in patients who experience cognitive AEs. All dose modifications in the NAVIGATOR study lead to improvement in all Grade ≥ 2 events, with a median time to improvement of [redacted] days. Patients who were given dose interruptions improved the fastest, with a median time to improvement of [redacted]days. These treatment holidays have also been demonstrated not

to impact outcomes, with patients receiving dose modifications having similar PFS to those that did not.[53] Blueprint is currently working with the Committee for Medicinal Products for Human Use on a risk management plan for use with avapritinib. This will help clinicians to minimize any risk in their use of avapritinib and to support them in the management of AEs. There are existing frameworks in place within NHS England that will also help to identify and manage these patients in clinical practice. As clinician experience and knowledge sharing with using avapritinib increases, and in particular with the use of dose modifications for patients with cognitive effects, a further improvement in patient management over time can be expected.

B.2.11. Ongoing studies

Follow up in the NAVIGATOR study is ongoing for survival.

The VOYAGER study is an open-label, randomized, Phase III study of avapritinib compared with regorafenib in patients with locally advanced, unresectable or metastatic GIST (advanced GIST), previously treated with imatinib and one or two other TKIs. This study includes a subgroup of patients with the *PDGFRA* D842V mutation; however, only 12 of these patients have been recruited (six in each treatment group), so no subgroup analysis is currently planned for this population.

B.2.12. Innovation

Avapritinib is 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 (see Section B.2.6). There are currently no effective treatment options available for these patients, and their choice is limited to burdensome, ineffective treatment with current TKIs or best supportive care – both of which are associated with limited life expectancy and poor quality of life – with the potential third option of being enrolled on an appropriate clinical trial, should one be available. The availability of avapritinib thus represents a clear step change in the management of unresectable or metastatic GIST for these patients.

While the majority of the clinical benefits of avapritinib should be captured within the quality-adjusted life year (QALY) calculation presented in Section B.3.4, the

psychological benefits of having an effective treatment option available to them for the first time are not captured; such benefits are of important value to the patients. In addition, patients with GIST and their caregivers are known to experience high levels of fear relating to cancer recurrence or progression (as discussed in Section B.1.3.2).[32] Therefore, having a treatment option that delays their progression will help to alleviate those fears and enhance HRQL, improvements that may also not be fully captured within the QALY calculation.

Clinical experts confirmed that avapritinib would be used as a first-line therapy for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation.[1] However, the NAVIGATOR study includes patients who were treated with avapritinib beyond first line. These patients are generally expected to be a sicker patient population and to have more advanced disease. It would also be expected that, as in other oncology indications, the benefits of treatment will decrease over subsequent lines of therapy. Therefore, the OS data from the NAVIGATOR study are likely to be conservative. The full OS benefit of treatment with avapritinib in clinical practice in England and Wales could therefore be expected to be greater than the data reported in this submission would suggest.

Caregiver burden is not currently captured within the economic model. Some caregivers for patients with GIST have been shown to experience a substantial burden, with significantly reduced mental health, less vitality, lower general health and high levels of distress.[33] Improving outcomes and reducing the burden on patients with GIST will also remove some of this burden from their caregivers, leading to greater societal benefits than have been captured within this submission.

HRQL data in unresectable or metastatic GIST are limited, particularly in the population with the *PDGFRA* D842V mutation. While the best available data were used within this submission (see Section B.3.4), and confirmation for this given by clinical experts,[1] as HRQL data were not captured within the NAVIGATOR study there remains uncertainty about whether the data that have been used will fully capture the treatment benefits of avapritinib. Therefore, there is the potential for avapritinib to improve HRQL beyond what is presented within this submission.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Summary and discussion of the available evidence to support avapritinib

Avapritinib is the first targeted treatment that is proven to be highly effective in patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation.

Avapritinib has demonstrated unprecedented levels of response for these patients, who would not be expected to respond to ECM. In the NAVIGATOR study, an ORR of [redacted]% (95% CI: [redacted]) was reported for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST, with [redacted]% of patients experiencing a CR, [redacted]% experiencing a PR and [redacted]% remaining in SD. Given the limitations of existing treatment options, as discussed in Section B.1.3, the CBR (the proportion of patients with confirmed CR/PR or SD lasting four or more cycles from first dose date) is an extremely important outcome to consider for this population. For the same patient population, the CBR in the NAVIGATOR study was [redacted]% (95% CI: [redacted]), and [redacted] patients had progressive disease as their best response to therapy – a complete step change in the treatment landscape for this population with substantial unmet need.

Responses observed during the NAVIGATOR study were extremely durable, with a median DoR of [redacted] months (95% CI: [redacted]); [redacted]% of responders were still in response at 24 months. Given that anticipated survival for these patients treated with ECM is currently approximately 13–15 months,[15-17] patients still being in response beyond 2 years is clearly a substantial benefit for this population.

Avapritinib has demonstrated long-term OS and PFS for patients with unresectable and metastatic *PDGFRA* D842V-mutated GIST, with median OS [redacted] and median PFS of [redacted] months for these patients in the NAVIGATOR study, after a median follow-up of [redacted] months. At 42 months, [redacted]% of patients were still alive and [redacted]% of patients remained in PFS. According to UK clinical experts,[5] with a median PFS of approximately 2 years, a median OS of > 5 years would be entirely plausible, using the example of first-line imatinib in the wider unresectable or metastatic GIST population.[54] This demonstrates the potential for significant long-term survival benefits with avapritinib for these patients.

The benefits of treatment with avapritinib are maintained beyond treatment discontinuation. Clinical experts with experience in using avapritinib have confirmed that patients experience prolonged response and disease control, even after stopping treatment.[55] The long-term benefits of avapritinib are apparent even in patients who may need to reduce doses, or take temporary treatment breaks due to AEs, with outcomes being maintained for these patients.[53]

Avapritinib shows significant improvements in survival outcomes compared with ECM with existing TKI therapies. In the IPW-adjusted analysis of BLU-285-1002, described in Section B.2.8, the estimated proportion of patients alive at 24 months in the avapritinib group was [redacted] that of the group treated with ECM ([redacted]% compared to [redacted]%, respectively). Median survival was [redacted] for avapritinib-treated patients (after a median follow-up of [redacted] months), compared with a median of only [redacted] months for those treated with ECM. This is supported by evidence from a naïve comparison of the data from Cassier et al. with those of the NAVIGATOR study,[17] which clinicians agreed were the most appropriate publicly available data to use for a naïve comparison (see Section B.2.8).[1] This comparison confirmed that treatment with avapritinib significantly increased patients' response to treatment ([redacted]% versus 0%), PFS (median [redacted] months versus 2.8 months) and OS (median [redacted] versus 14.7 months). UK clinical experts confirmed that the outcomes presented in the study by Cassier et al. are reflective of what they would expect to see for unresectable or metastatic GIST patients with the *PDGFRA* D842V mutation,[1] and therefore the results presented in the NAVIGATOR study represent a statistically and clinically significant improvement for these patients.

The safety profile of avapritinib is well described with acceptable levels of toxicity that are comparable with ECM (Section B.2.10). The key AESI is cognitive effects, which were experienced by [redacted]% of patients in the NAVIGATOR study. However, most of these events were mild, with no impact on activities of daily living and all of the more serious events improved within a median of 12.0 days.

B.2.13.2. Strengths and limitations of the evidence base

The evidence base used to support avapritinib has several strengths. Given the ultra-orphan nature of the population of interest, the NAVIGATOR study contains an exceptionally large cohort of patients in the population directly relevant to the

decision problem. Clinical opinion confirmed that the population treated in the NAVIGATOR study was reflective of the population anticipated to be treated with avapritinib in clinical practice in England and Wales. The outcomes used in the trial are relevant to patients and consistent with those that would be captured as part of standard practice in NHS England; clinical opinion confirmed that the results seen in the NAVIGATOR study would be expected to be the same for these patients treated in England and Wales.[1, 5]

The NAVIGATOR study demonstrates compelling results in a condition with significant unmet medical need, no effective standard therapy and short expected survival. The fact that [redacted]% of patients are still alive at 42 months (compared with median survival of approximately 13–15 months with ECM) is a significant benefit. Also, as discussed previously, an estimated PFS rate of [redacted]% at 24 months shows that there is potential for significant long-term survival benefits, with [redacted]% remaining alive and progression free at 42 months. Also, as discussed in Section B.2.12, the data from the NAVIGATOR study includes patients treated beyond first line, where avapritinib would be used in clinical practice, which means that the survival data from this study are likely to be conservative. However, as a result of this high level of efficacy of avapritinib, median OS [redacted] in the NAVIGATOR study. Therefore, while the fact that avapritinib represents a step change in the treatment paradigm for these patients is clear, uncertainty surrounding the full extent of the health benefits remains.

The NAVIGATOR study was conducted as a single-arm study, which makes comparison with ECM challenging. However, as patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation have no other effective treatment option, an RCT would be considered unethical, and therefore a single-arm study is the most appropriate study design. To mitigate some of the difficulties of deriving evidence from a single-arm study, BLU-285-1002 was specifically designed to be used as a historical control for efficacy studies of avapritinib. The availability of patient-level data from this study was a significant advantage in being able to provide an appropriate comparison to ECM (Section B.2.9). Simon et al.[56] suggest the following criteria for judging whether a single-arm study can support traditional approval, which the data for avapritinib support:

- The drug mechanism of action is supported by strong scientific rationale or preclinical data
  - Avapritinib has demonstrated biochemical in vitro activity on the *PDGFRA* D842V and *KIT* D816V mutants associated with resistance to imatinib, sunitinib and regorafenib[2]
- The drug is intended for a well-defined patient population
  - The intended population is a well-defined group of patients identified by mutational testing usually performed at diagnosis as part of current clinical practice and recommended in current clinical guidelines[7, 8]
- The drug produces substantial, durable tumour responses that clearly exceed those offered by any existing available therapies
  - The results presented in Sections B.2.6 and B.2.8 and summarized at the beginning of Section B.2.13 show that avapritinib demonstrates a substantial and durable tumour response that clearly outweighs the outcomes experienced by patients treated with ECM, where there are currently no effective treatment options
- The benefits outweigh the risks
  - The majority of AEs that occurred within the study were well defined, generally reversible and manageable using current NHS frameworks, with no apparent long-term consequences. The key AE of special interest, cognitive AEs, were mostly Grade 1 events that did not impact activities of daily living, and all Grade ≥ 2 events improved within a median of 12 days. Given that these patients have no other treatment options and poor expected survival without avapritinib, the benefits of avapritinib clearly outweigh the risks

Limited HRQL data are available for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, and HRQL data for avapritinib-treated patients were not captured in the NAVIGATOR study. Therefore, in order to ensure that the HRQL data used to inform the model were appropriate and reflective of UK patients, utility values were taken from published literature and tested with UK clinicians.[1] These are presented in Section B.1.3 and discussed in more detail in relation to the economic model in Section B.3.4. As no HRQL data were captured specifically for these patients within the NAVIGATOR study, there remains some uncertainty about whether the extent of the benefits of avapritinib have been fully captured; it is

possible that these patients treated in clinical practice in NHS England may actually experience greater improvements in their HRQL.

There are a number of difficulties in comparing avapritinib with established clinical management. Given the rarity of unresectable or metastatic GIST, and the limited number of patients with the *PDGFRA* D842V mutation, extremely limited data are available for comparison. In order to ensure the most appropriate source of evidence was used for ECM, patient-level data from the BLU-285-1002 study were used to perform an IPW-adjusted comparison to the NAVIGATOR study. This ensured that the data used for the comparison to inform the economic model were weighted based on the key baseline characteristics of the NAVIGATOR study in order to reduce the bias in these data. The concurrence of the results with the data published by Cassier and colleagues support the face validity of this approach.[15]

B.2.13.3. Generalizability

The NAVIGATOR study was conducted in 19 centres, with patients enrolled at 17 of them, including eight in the US, eight in Europe and one in Asia. This included one site in the UK: the Royal Marsden Hospital in London, which recruited [redacted] patients with the *PDGFRA* D842V mutation ([redacted]%). This is a large proportion of the population for an international study and increases the likelihood that the study results are generalizable to a UK population.

The median age in the NAVIGATOR study was 64.0 years. This is in line with clinical practice, where GIST patients are most commonly aged between 60 and 65.[11] UK clinicians agreed that the patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST treated in the NAVIGATOR study were likely to be reflective of patients who would be eligible for treatment with avapritinib in the UK, and that the NAVIGATOR study population was generally reflective of patients who would be seen in clinical practice.[1] Therefore, the treatment outcomes seen for patients with the *PDGFRA* D842V mutation in the NAVIGATOR study would be expected to be generalizable to patients treated in NHS England, with significant improvements in response rates, PFS and OS for those patients.

The NAVIGATOR study results presented within the submission document (and used in the economic model) include patients treated at doses other than that which

is expected to be used in clinical practice (300 mg once daily). However, comparison of the outcomes between the different dose groups (see Appendix L) shows that there were no significant differences in outcomes dependent on dose. Given the ultra-orphan nature of the condition and limited patient numbers, it was therefore considered appropriate to use data from all patients with *PDGFRA* D842V-mutated disease regardless of starting dose, in order to maximize the evidence that was available.

B.2.13.4. Avapritinib as an end-of-life therapy

Table 30 presents the evidence to support avapritinib as an end-of-life therapy, in line with the NICE criteria. Patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation are known to be insensitive to current treatment options. With ECM, these patients have median OS as low as [redacted] months.[17] This means that for the majority of these patients, their expected life expectancy is well below the 24 months specified by NICE. At 24 months, based on the IPW-adjusted analysis of BLU-285-1002, [redacted]% of patients were still alive. In the base case for the economic model, mean OS for patients treated with established clinical management is 23.72 months. This further supports the fact that life expectancy for these patients is expected to below 24 months.

Median OS was [redacted] in the NAVIGATOR study as the OS data are not yet mature. However, at 18 months of follow-up (5.4 months beyond the median survival of [redacted] months reported in the IPW-adjusted analysis of BLU-285-1002) [redacted]% of patients with the *PDGFRA* D842V mutation in the NAVIGATOR study were still alive, with [redacted]% still alive at 42 months. This suggests that avapritinib is likely to provide an extension to life substantially greater than the 3 months specified by NICE for the majority of patients with the *PDGFRA* D842V mutation. The economic model presented in Section B.3. shows that avapritinib would provide an additional [redacted] life-years for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, compared with established clinical management (Appendix J.2.). Therefore, avapritinib should be considered as an end-of-life therapy.

Table 30: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Mean survival:** 23.72 months **Median survival estimates:** BLU-285-1002 IPW-adjusted: [redacted] months[17] Cassier et al., 2012: 14.7 months[15] **24 month survival estimates:** BLU-285-1002 IPW-adjusted: [redacted]%[17] Cassier et al., 2012: NR[15]	**BLU-285-1002** Section B.2.9.2.2; Page 54 and Section B.3.7.1, Page 136 **Cassier et al., 2012** Appendix D.1; Pages 35–36
There is sufficient evidence to indicate the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**Median survival estimate:** [redacted] **24 month survival estimate:** [redacted]% **42 month survival estimate:** [redacted]% **Incremental LY gains:** [redacted]	Section B.2.6.1, Pages 38–40 and Appendix J.2, Page 89
Key: ECM, established clinical management; IPW, inverse probability weighting; LY, life year; NHS, National Health Service; NR, not reported; OS, overall survival.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify cost-effectiveness studies assessing the treatment of patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation. Full details of the search are provided in Appendix G.

Only one study relating to the relevant population was ultimately included for data extraction.[57] This study explored costs from the perspective of the Belgian healthcare system and was therefore not considered further. Table 31 (in Section B.3.2.6) further describes previous NICE committee key economic analysis decisions for imatinib, sunitinib and regorafenib. Although these are appraisals for general unresectable or metastatic GIST, some aspects of these technology appraisals are relevant to this decision problem (e.g. resource use, utilities). These appraisals were used, where appropriate, to formulate the assumptions used in this submission, allowing the fairest possible comparison between avapritinib and ECM with the available data.

B.3.2. Economic analysis

B.3.2.1. Reference to previous NICE technology appraisals for gastrointestinal stromal tumour

No NICE health technology assessments (HTAs) evaluating the efficacy of treatments for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation were identified. However, we are aware of three previous NICE HTAs, and one HTA update, of treatments for unresectable or metastatic GIST (TA86, TA179, TA488, and TA209 respectively).[29, 44, 58] Due to the extreme rarity of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST, information and assumptions contained in these technology appraisals have been leveraged within our modelling approach. The primary aspects that have to some extent been

replicated or influenced by previous NICE GIST technology appraisals, unless otherwise stated, include:

- Aspects feeding into the conceptual model (covered below)
- Clinical inputs (see Section B.3.3)
- Health state utility values (see Section B.3.4)
- Healthcare resource use (HCRU; see Section B.3.5)

Use of these sources imposes several assumptions on the cost-effectiveness model; these assumptions cannot be avoided, given the lack of any alternative evidence for unresectable or metastatic *PDGFRA* D842V-mutated GIST. All modelling assumptions are summarized in Table 60, and are provided alongside summary justifications.

B.3.2.2. Use of a de novo cost-effectiveness model

No health economic cost-effectiveness models concerned with the unresectable or metastatic *PDGFRA* D842V mutation population were identified and available for re-use in this context. Furthermore, cost-effectiveness models used in previous GIST technology appraisals are not usable in the unresectable or metastatic *PDGFRA* D842V mutation context. This is because of the difference in the decision problem when looking at an intervention used at the beginning of a treatment pathway, and because of the lack of evidence available in this rare mutation. Finally, according to the literature and clinical testimony, the *PDGFRA* D842V mutation is known to confer resistance to all approved treatments of unresectable or metastatic GIST, resulting in a complete or near-complete absence of efficacy in this specific population.[1, 7, 15, 59] Currently available TKIs are highly ineffective for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation. As a result, a de novo model was constructed to estimate the clinical and economic outcomes specific to this patient group.

B.3.2.3. Patient population

The population included in the economic analysis, in line with the expected licensed indication, is adult patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation.

The patient population for unresectable or metastatic *PDGFRA* D842V-mutated GIST is extremely small. GIST is a relatively rare cancer, with an unadjusted incidence of approximately 1–1.5/100,000 patients per year.[11, 39] Most patients do not reach a metastatic or unresectable state, and the *PDGFRA* D842V mutation occurs in 1–2% of these patients. Consequently, *PDGFRA* D842V-mutated unresectable or metastatic GIST is likely to occur in approximately five patients in England and Wales each year.[1] The patient population is described in more detail in Section B.1.3.1.

B.3.2.4. Treatment pathway

As outlined in Section B.1.3.3, the relevant comparators for avapritinib in unresectable or metastatic *PDGFRA* D842V-mutated GIST are imatinib (first line), sunitinib (second line) and regorafenib (third line), based on NICE guidance and input from clinical experts.[1] Henceforth, these lines of therapy are referred to as first line, second line and third line, respectively. Most clinical experts consulted in a clinical survey agreed that, were avapritinib to be made available in England and Wales, nearly all patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in England and Wales would be treated with avapritinib until treatment failure.[1]

Following treatment failure due to lack of response, intolerance or progression, clinicians would be faced with little to no incentive to prescribe post-avapritinib patients with non-targeted TKIs. Continuing to treat post-avapritinib patients with non-targeted TKIs would expose them to toxicity without any expectation of clinical benefit, and would likely not form part of standard of care if avapritinib is introduced at first line.[1] For this reason, the appropriate comparison between treatment arms is avapritinib followed by no TKI treatment, as opposed to the sequence of TKIs currently used to treat patients who have unresectable or metastatic *PDGFRA* D842V-mutated GIST.

B.3.2.5. Trial evidence

B.3.2.5.1. Avapritinib

The unresectable or metastatic *PDGFRA* D842V-mutated GIST population within the ongoing Phase I, including a dose escalation and a dose expansion phase, single-arm, open label, multicentre clinical trial, NAVIGATOR, consists of 56 patients at

baseline, separated into three baseline dosing groups. Section B.2.2 and Appendix L.1 provide detailed summary information of baseline characteristics. Of the five clinicians consulted in a clinical survey, 100% agreed that the patients in the NAVIGATOR study are reflective of the patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in clinical practice in England and Wales.[1] Furthermore, as described in Section B.2.2, ToT, PFS and OS do not appear to be associated with statistically significant differences across the different avapritinib doses used in NAVIGATOR. Consequently, to ensure that the best and richest data available are used for the cost-effectiveness analysis, we have included data from all 56 patients who have unresectable or metastatic GIST with the *PDGFRA* D842V mutation.

B.3.2.5.2. Established clinical management

A retrospective chart-study (BLU-285-1002) was conducted to track the clinical outcomes of previously treated adult patients with confirmed *PDGFRA* D842V mutation-driven GIST in real-world practice.[60] This study included 22 patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST and had a maximum follow-up duration of 204 months.

The baseline characteristics of the patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation within BLU-285-1002 do not match those of the equivalent population in NAVIGATOR. When re-baselining the BLU-285-1002 survival data to the first TKI received for unresectable or metastatic disease, the baseline characteristics are still unbalanced between the samples (See Table 15). Consequently, it cannot be expected that the original outcomes reported directly in BLU-285-1002 are valid for a cost-effectiveness estimate of avapritinib without further analysis to control for differences in patient characteristics. However, as patient-level data are available for both the NAVIGATOR and BLU-285-1002 studies in the appropriate patient population, IPW was used to control for differences. This indirect comparison method was implemented in line with NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 17 and 18;[61, 62] a more detailed explanation of the IPW method is given in Section B.2.9 and Appendix N.3. For brevity, we henceforth refer to the propensity score weighted data sets as IPW NAVIGATOR and IPW BLU-285-1002, or IPW data sets.

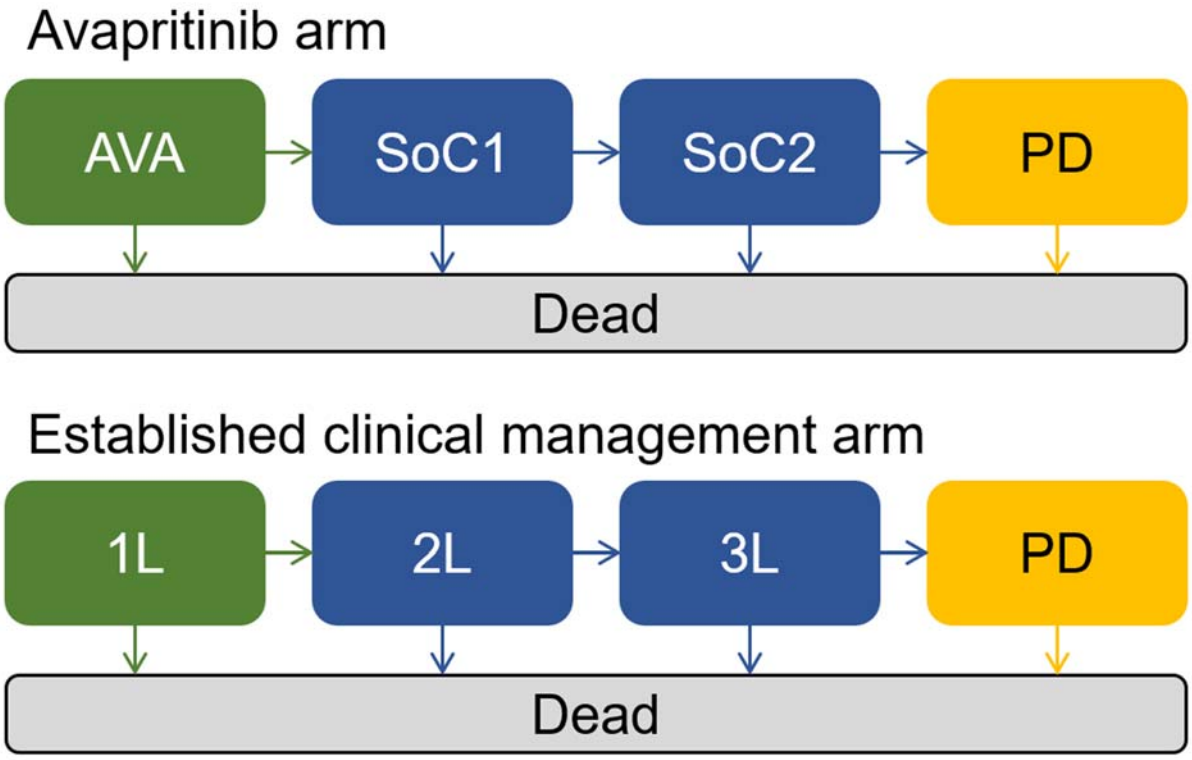
As discussed in Section B.2.9.1, the best alternative to the IPW analysis is a naïve comparison between NAVIGATOR and Cassier et al. However, the article by Cassier et al. does not provide patient characteristics for the unresectable or metastatic *PDGFRA* D842V mutation population, meaning we do not have any basis to suggest similarity of (or adjust for) baseline patient characteristics. We therefore argue that the IPW BLU-285-1002 data provide the richest, most up-to-date and most robust comparator data available.

Section B.2.9 and Appendix N provide more detailed analysis of the difference between IPW and non-IPW clinical endpoints from NAVIGATOR and BLU-285-1002.

B.3.2.6. Model structure

Our cost-effectiveness model uses a cohort partitioned survival structure, focusing on the ability of avapritinib to inhibit disease progression, which is in turn associated with an OS benefit. The model tracks a cohort of patients through the existing and prospective treatment pathways (categorized into a series of discrete health states), should avapritinib be approved as a treatment for unresectable or metastatic *PDGFRA* D842V-mutated GIST. The individual health states per arm and a visualization of the flow of patients through the model are provided in Figure 12.

Figure 12: Structure of cost-effectiveness model



Key: 1L, first line; 2L, second line; 3L, third line; AVA, avapritinib; PD, progressive disease; SoC, standard of care.
Notes: SoC1 and SoC2 differ from 2L and 3L only in terms of treatment cost. All other parameters are identical. Probability of transition from SoC1 to SoC2 is the same as probability of transition from 2L to 3L, and probability of transition from SoC2 to PD is the same as probability of transition from 3L to PD in the base case analysis.

To summarize, patients in the ECM arm are treated with three successive lines of therapy: first line, second line and third line. Upon progression from third line, the surviving cohort is categorized as having progressive disease, which at this time is associated with no licensed therapy. Each progressive line of therapy is associated with increased HCRU costs and lower HRQL compared to all previous states, to capture the worsening of the disease as patients traverse the treatment pathway.

Similarly, patients in the avapritinib arm are treated at baseline with avapritinib. As stated above, most clinical experts agreed that patients failing avapritinib treatment would receive best supportive care and not be subsequently treated with non-targeted TKIs.[1] However, these patients still have a progressive disease, and an appropriate cost-effectiveness model must therefore capture further disease stages beyond initial progression. Therefore, upon discontinuation with avapritinib, patients

cycle through two standard-of-care states, SoC1 and SoC2. Patients in the SoC1 and SoC2 health states are assigned the same HCRU costs and utilities as those in the second line and third-line health states from the ECM arm. However, patients in SoC1 and SoC2 have no cost associated with TKIs and no treatment emergent adverse events. Finally, patients in both arms who remain alive and experience disease progression at SoC2 or 3L transition into the progressive disease health state, which is associated with a lower health state utility value and higher HCRU.

The structure of the cost-effectiveness model is similar to the approaches used in previous NICE technology appraisals in unresectable or metastatic GIST (summarized in Table 31), with some key differences. Previous NICE technology appraisals TA86, TA179 and TA488 focused on first-line, second-line and third-line GIST treatments, respectively;[29, 44, 58] in contrast, the cost-effectiveness model for avapritinib must consider the whole treatment pathway for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST. Across these technology appraisals, patient HRQL in the 'progression-free' health state is lower for those treatments appraised at a later line, which reflects the progression of the disease (See Table 50). Likewise, the HCRU associated with care for patients (other than TKI treatments received) reflects worsening of the disease. As these further stages of unresectable or metastatic *PDGFRA* D842V-mutated GIST are associated with an increasing burden of disease and distinct levels of HCRU, it is important that they are captured in an economic model. In a clinical survey, 100% of clinicians agreed that the utility values shown in Table 50 are likely to be reflective of the HRQL of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in UK clinical practice, before and after the introduction of avapritinib.[1] This provides an opportunity to leverage the previous technology appraisals in GIST to establish the progression-free health-state utility and resource use of patients as they traverse the three lines of currently available therapy. Details of the modelling mechanics behind this are provided in Sections B.3.3.2.1 and B.3.3.3.1.

Table 31: Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA8629	TA17944	TA48858	Chosen values	Justification
Time horizon	10 years	6 years	40 years	40 years	Captures all feasible clinically relevant differences between the arms
Treatment waning effect	No	No	No	Yes	See Section B.3.3
Definition of health states	PFS, PPS, Dead	PFS, PPS, Dead	PFS, PPS, Dead	First line, second line, third line, progressive disease, dead	Measures of progression in TA86, TA179 and TA488 are relative to the size of the original tumour (i.e. proportional change in tumour size), and therefore PFS in subsequent lines cannot be directly compared. The best available method for tracking the progression of GIST in these patients, given current treatment pathway and available evidence is using available progression-free survival data at first line, second line and third line. This allows the relevant treatment costs and patient HRQL to be captured in a manner sufficient for health economic decision making.
Dose adjustments	Not reported	Uses reported RDI values for sunitinib	Uses the mean actual treatment dose from the GRID study	All TKI costs are adjusted for relative dose intensity and/or dose breaks	Captures the expected treatment acquisition costs per patient.
Source of utilities	Mapping of ECOG data from the CST1571-B2222 trial to	EQ-5D data from the A6181004 study	EQ-5D from the GRID study[31]	NICE TAs 86, 179, 488	Previous unresectable or metastatic GIST NICE TAs are the best available source of information on the HRQL of UK patients with *PDGFRA* D842V-mutated GIST

Factor	Previous appraisals			Current appraisal	
	TA8629	TA17944	TA48858	Chosen values	Justification
	EQ-5D® data via a questionnaire returned by three clinicians				
Source of resource use costs	Not reported	Cancer physician panel	2013 physician resource use survey of 15 GIST medical oncologists in England and Wales	NICE TAs 86, 179, 488, updated with a survey conducted with 5 GIST medical oncologists in England and Wales	Previous unresectable or metastatic GIST NICE TAs are the best available source of information on the HCRU of UK patients with *PDGFRA* D842V-mutated GIST. We have also conducted clinical validation of the high-cost resource use values[1]

Key: ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; HCRU, healthcare resource use; HRQL, health-related quality of life; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; RDI, relative dose intensity; TA, technology appraisal; TKI, tyrosine kinase inhibitor.

B.3.2.7. Intervention technology and comparators

B.3.2.7.1. Avapritinib

The avapritinib arm is implemented in the model as per the expected marketing authorization (unresectable or metastatic GIST with the *PDGFRA* D842V mutation). However, clinical experts have indicated that if avapritinib is authorized and available for use, imatinib, sunitinib and regorafenib will not be used in patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST. Therefore, as discussed above, the avapritinib arm consists of first-line avapritinib followed by no TKI in subsequent lines.

Avapritinib is expected to be licensed at a dose of 300 mg/day. The cost of bottles of tablets is the same regardless of the per-tablet dose, meaning that dose adjustments do not affect the cost of treating a patient (See Table 51).

However, dose breaks still affect the cost of treatment, as these extend the period for which a bottle of tablets will last. This is reflected in the cost-effectiveness model per Table 32 below.

Table 32: Frequency of dosing in avapritinib patients, NAVIGATOR

Dosed days (mean)	Duration of the treatment (mean)	Multiplier applied to monthly cycle cost	Source
377.2	[redacted]	[redacted]	NAVIGATOR clinical data
Notes: 0.87 is the mean of each individual relative dose intensity, whereas 0.88 is equal to 377.2/427.8.			

No treatment discontinuation rule is expected for avapritinib. Recording of ToT is discussed in Section B.3.3.

B.3.2.7.2. Established clinical management

The current ECM for unresectable or metastatic GIST patients in the UK is first-line imatinib, second-line sunitinib and third-line regorafenib, followed by best supportive care as supported by clinical experts.[1] Currently this does not vary by *PDGFRA* D842V mutation status, as there is no treatment specifically for patients with this

mutation. Therefore, the TKI costs associated with those lines of therapy have been assumed to be the cost of imatinib, sunitinib and regorafenib, respectively.

Cost of therapies

Although a cost for generic imatinib is listed on the UK drugs and pharmaceutical electronic market information tool (eMIT) database, generic imatinib is not currently licensed by EMA for use in the treatment of unresectable or metastatic *PDGFRA* D842V mutation GIST.[63-65] Further, it is not expected to become available to unresectable or metastatic *PDGFRA* D842V mutation GIST patients within the timeframe of this decision problem. Consequently, the cost of branded imatinib is used within the model to capture TKI costs for first-line unresectable or metastatic *PDGFRA* D842V mutation GIST patients. To our knowledge, no generics are available for sunitinib or regorafenib within the unresectable or metastatic *PDGFRA* D842V-mutated GIST indication. Please see Section B.3.5 for details on the costs of comparator therapies.

B.3.3. Clinical parameters and variables

B.3.3.1. Curve fitting procedure

The data deriving from the NAVIGATOR study for avapritinib are immature, necessitating the use of survival extrapolation to produce an estimated mean survival to be used for modelling. Per the NICE reference case, the advice provided in NICE DSU TSD 14[66] has been used to perform survival analysis, and subsequently to select the most appropriate survival extrapolations. The models considered were exponential, Weibull, log-normal, log-logistic, and Gompertz.

Each of these five models were evaluated for every individual Kaplan–Meier survival estimate considered in the survival analysis, in terms of the following:

- Visual fit of the survival extrapolation compared to the available Kaplan–Meier data, within the period of follow-up
- Appraisal of the long-term extrapolated tail of both log-cumulative hazard and conditional probability plots, when extrapolating out to the model time horizon
- Consideration of the long-term absolute survival extrapolation (the tail), specifically plausibility of 1-, 2-, 5- and 10-year survival estimates

- Consideration of statistical fit for each survival model, using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)

The base case survival results were validated with UK clinical experts. Further details of model selection for each clinical outcome are provided below.

B.3.3.2. Overall survival

B.3.3.2.1. Avapritinib

Overall survival in the avapritinib arm was captured and extrapolated based on the information available from the NAVIGATOR trial, as of 17 January 2020. The base case uses the IPW NAVIGATOR and BLU-285-1002 data sets, and this is reflected in all the survival sections to follow.

Waning of treatment effect on overall survival

It is unlikely that any of the treatments considered in this decision problem maintain an indefinite treatment effect when a patient stops treatment. Furthermore, the time on treatment data for avapritinib are incomplete. Therefore, an appropriate cost-effectiveness model must account for potential loss of treatment effect upon treatment discontinuation.

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 (see Section B.2.9.1). Consequently, the most realistic possible 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.

We consulted clinical experts about the loss of treatment effect upon avapritinib discontinuation in an advisory board and in clinical validation interviews. The clinical experts supported a gradual loss of treatment effect over the course of 60 months after discontinuation, rather than a patient losing all survival benefit immediately. To reflect this, we have incorporated into the cost-effectiveness model a gradual movement of OS hazard from that of the avapritinib arm to that of the ECM arm upon discontinuation from avapritinib treatment. To expand, the gradual treatment waning

approach used calculates the final per-cycle probability of death $TP_{(t)}$ as a function of time since discontinuation for each sequential cohort of patients that discontinues (i.e. at every model cycle). This was achieved through the introduction of a 'tunnel-state' to the cost-effectiveness model, which lasts for 60 cycles (i.e. months) in the base case. In each cycle within this tunnel, the final probability of death $TP_{(t)}$ is determined by tracking time since discontinuation using linear interpolation. 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 is explained in more detail in Appendix O.1.

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.[55]

Overall survival data

The OS analysis from NAVIGATOR used censors for discontinuation events. It therefore captures mortality only for those patients still receiving avapritinib (i.e. in the avapritinib state and still on treatment, see Figure 12). This mortality is then only applied to those patients remaining on avapritinib and in part to those who are still benefitting from avapritinib beyond discontinuation, as explained above. Figure 13 shows the original and IPW Kaplan–Meier data, and demonstrates that IPW had no discernible effect on the original Kaplan–Meier data.

Figure 13: Overall survival Kaplan–Meier – avapritinib, censoring for discontinuation before death

Key: IPW, inverse probability weighting.

Figure 14 shows the visual fit of all parametric models considered, over the follow-up period for NAVIGATOR. Given the low number of events in the Kaplan–Meier data, it is difficult to evaluate the fit of the parametric models.

Figure 14: Overall survival models during trial follow-up – avapritinib, censoring for discontinuation, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

The long-term plausibility of each of the parametric models was considered alongside the underlying hazard (see Figure 15 and Figure 16). Table 33 presents the OS estimates over time.

Figure 15: Overall survival models extrapolated to 40 years – avapritinib, censoring for discontinuation, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Figure 16: Overall survival log-cumulative hazard – avapritinib, censoring for discontinuation, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Table 33: Overall survival estimates at set time points – avapritinib, censoring for discontinuation, IPW adjusted

Time	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40.0 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: IPW, inverse probability weighting.

Table 34 presents the statistical fit of each avapritinib OS parametric model. The AIC and BIC statistics are close in range and largely all within 5 values of each other, indicating no notable difference in statistical fit across models.

Table 34: Overall survival statistical fit – avapritinib, censoring for discontinuation, IPW adjusted

Fit statistics	Akaike information criterion	Bayesian information criterion
Exponential	17.84	19.87
Weibull	19.81	23.86
Gompertz	20.58	24.63
Log-normal	20.93	24.98
Log-logistic	21.12	25.17

Key: IPW, inverse probability weighting.

As the individual observations are weighted in the IPW analysis, AIC and BIC are less reliable (weights are provided in Appendix N.2). 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.

A log-normal model is used in the base case. When presenting the results of our base case model to Professor Ian Judson and Dr Robin Jones, both provided support, suggesting that the final OS estimates were clinically plausible.

B.3.3.2.2. Established clinical management

Among the data sources presenting OS for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST for the ECM arm, an IPW analysis of the retrospective natural history study BLU-285-1002 appears to provide the most suitable ECM survival data and was used in the base case for the reasons outlined in Section B.2.9.1.

When baseline characteristics of patients studied in Cassier et al. were presented to clinical experts, there was a consensus that these were reflective of the patients seen in clinical practice in England and Wales who would be eligible for avapritinib.[1] Therefore, a scenario is included in the cost-effectiveness model using survival data from Cassier et al. in the ECM arm. The curve selection process based on Cassier et al. is provided in Appendix P.

Parametric models fit to the IPW BLU-285-1002 data are shown in Figure 17 (model fits to the observed data) and Figure 18 (long-term model extrapolations). The curves show reasonable fit to most of the Kaplan–Meier data yet begin to underestimate survival towards the tail as numbers at risk decrease. Gompertz is the exception to this, with plateaued survival from approximately 100 months. The exponential model is considered to have the poorest visual fit to the Kaplan–Meier data overall, overestimating survival until approximately 20 months yet underestimating survival from 40 months onwards.

Figure 17: Overall survival models during study follow-up – established clinical management, IPW BLU-285-1002

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Figure 18: Overall survival models extrapolated to 40 years – established clinical management, IPW BLU-285-1002

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

The log-cumulative hazard plots for each of the models are shown in Figure 19. OS estimates over time are given in Table 35. Table 36 presents the statistical fit of each IPW OS parametric model fitted to the data from BLU-285-1002. The Weibull model has the best statistical fit according to both the AIC and BIC statistics.

Figure 19: Overall survival log-cumulative hazard – established clinical management, IPW BLU-285-1002

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Table 35: Overall survival estimates at set time points – established clinical management, IPW BLU-285-1002

Time	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0.0 years	[redacted]				
0.5 years					
1.0 years					
2.0 years					
5.0 years					
10.0 years					
20.0 years					
40.0 years					
Key: IPW, inverse probability weighting.					

Table 36: Overall survival statistical fit – established clinical management, IPW BLU-285-1002

Fit statistics	Akaike information criterion	Bayesian information criterion
Exponential	373.12	374.06
Weibull	343.73	345.62
Gompertz	571.38	573.27
Log-normal	567.17	569.06
Log-logistic	570.05	571.94
Key: IPW, inverse probability weighting.		

The Weibull parametric curve is applied at base case in the model because it has the best statistical fit as well as good visual fit to the observed data and in the long term.

Mean and median survival of the observed BLU-285-1002 Kaplan–Meier data and each of the parametric models are shown in Table 37. Median survival is below 2 years in both the observed Kaplan–Meier data and in the fitted Weibull model, and mean survival for the Weibull model is only just above 2 years.

Table 37: Mean and median extrapolated overall survival – established clinical management, IPW BLU-285-1002

	Mean, years	Median, years
Kaplan–Meier	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Key: IPW, inverse probability weighting.		

B.3.3.2.3. End-of-life criteria

Rationale for the consideration of avapritinib as an end-of-life therapy is provided in Section B.2.13.4. In addition to this, all parametric extrapolations of both BLU-285-1002 and Cassier et al. data give median survival values of considerably below 2 years. While mean survival ranges between 1.8 and 2.1 years depending on the model selected, models providing mean survival estimates at or above 2 years likely underestimate patient hazard in the long term. Furthermore, clinical consultations on the life expectancy of patients with unresectable or metastatic *PDGFRA* D842V mutation GIST in UK clinical practice have suggested a survival of under 2 years. Consequently, it is likely that the treatment is indicated for patients with a short life expectancy, normally less than 24 months. Regarding the survival benefit of avapritinib, the extrapolation of survival produces an OS estimate of approximately 8 years. All estimates imply an OS benefit associated with avapritinib well in excess of 3 months. In conclusion, there is strong evidence that avapritinib for the treatment of unresectable or metastatic *PDGFRA* D842V-mutated GIST should be considered an end-of-life treatment for decision making.

B.3.3.3. Progression-free survival

For avapritinib patients, data from the NAVIGATOR study capturing PFS are available. 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. In addition, the availability of patient-level data 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.

B.3.3.3.1. Avapritinib

First line

PFS in the avapritinib arm was captured and extrapolated based on the information available from IPW NAVIGATOR data, as of 17 January 2020 (see Figure 20).

Figure 20: Progression-free survival Kaplan–Meier – avapritinib, censoring for death: IPW adjusted versus unadjusted

Key: IPW, inverse probability weighting.

Figure 21 shows the visual fit of all parametric models considered, over the follow-up period for NAVIGATOR. Each model displays a similar fit with respect to the Kaplan–Meier data. The exponential model may be considered to underestimate the Kaplan–Meier data until approximately 15 months.

Figure 21: Progression-free survival models during trial follow-up – avapritinib, censoring for death, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

The long-term extrapolations of each model are presented in Figure 22 and Table 38. In addition, the log cumulative hazard plot of Figure 23 demonstrated the long-term hazard of progression for each model. Gompertz presents the most pessimistic extrapolation of [redacted] years. Finally, Table 39 shows estimated mean and median survival. All means are considerably higher than medians, suggesting a reducing hazard over time.

Figure 22: Progression-free survival models extrapolated to 40 years – avapritinib, censoring for death, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Table 38: Progression-free survival estimates over time – avapritinib, censoring for death, IPW adjusted

Time	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0.0 years					
0.5 years					
1.0 years					
2.0 years					
5.0 years					
10.0 years					
20.0 years					
40.0 years					

Key: IPW, inverse probability weighting.

Table 39: Progression-free survival estimated survival by model – avapritinib, censoring for death, IPW adjusted

	Mean, years	Median, years
Kaplan–Meier		
Exponential		
Weibull		
Gompertz		
Log-normal		
Log-logistic		

Key: IPW, inverse probability weighting.

Figure 23: Progression-free survival – avapritinib, log-cumulative hazard extrapolations

Key: KM, Kaplan–Meier.

The statistical fit of each of the models to the observed PFS data was then considered with respect to the AIC and BIC values in Table 40. 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.

Table 40: Progression-free survival statistical fit – avapritinib, censoring for death, IPW adjusted

Fit statistics	Akaike information criterion	Bayesian information criterion
Exponential	125.76	127.79
Weibull	124.00	128.05
Gompertz	156.34	160.39
Log-normal	151.26	155.31
Log-logistic	152.63	156.68
Key: IPW, inverse probability weighting.		

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. Exponential is presented in scenario analysis.

When presenting the results of our base case model to Professor Ian Judson and Dr Robin Jones, both provided support, suggesting that the final PFS estimates were clinically plausible.

Subsequent lines

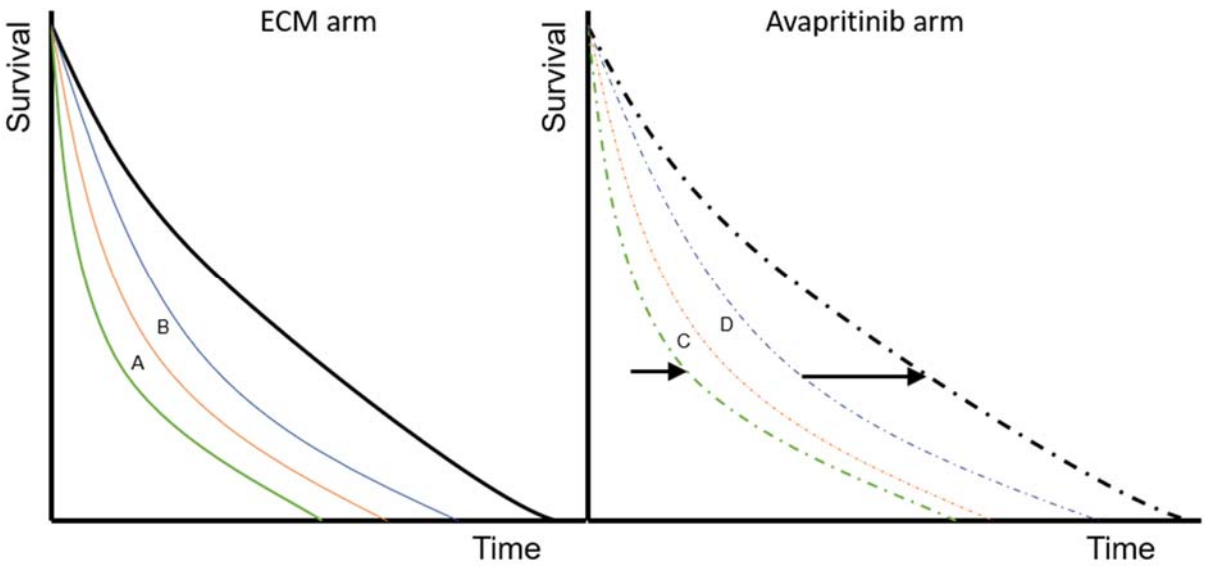
We are not aware of any clinical data describing disease progression for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST at later lines of therapy after an initial treatment with avapritinib. The NAVIGATOR also did not capture progression of disease in those patients beyond first line. Consequently, there is currently no reliable empirical basis on which to suggest that avapritinib treatment impacts disease progression at later lines or disease stages. In the base case of our model, therefore, the per-cycle probabilities of progression in the SoC1 and SoC2 states are set as equal to the per-cycle probabilities of progression in the second-line and third-line states in the ECM arm, based on their respective clinical data sources.

Within the survival analysis and cost-effectiveness model implementation, several steps are necessary to achieve this. These are summarized below and in Figure 24:

- PFS analysis for the ECM arm at first line, second line and third line must be censored for death events
  - The only remaining event possible in the PFS curve is then progression before death
  - The hazard associated with a parametric extrapolation of this curve represents only the probability of progression (ignoring the probability of death)
- The per-cycle probability of progression and death are now separated
  - This allows manipulation or re-use of only the probability of progression in the ECM arm, without also affecting the per-cycle probability of death
- Every model cycle, the probability of only progression at second line and third line from the ECM arm is combined with the avapritinib mortality rate (derived from the associated OS data)

- This allows the probability of progression to be held constant across arms and the probability of death to be linked directly to OS data

Figure 24: Example of structural assumption: equal rates of subsequent progression across arms



Key: ECM, established clinical management; IPW, inverse probability weighting; SoC, standard of care.
Notes: Solid lines: sourced entirely from ECM arm (IPW BLU-285-1002) data. Dash-dot lines: sourced from a combination of IPW NAVIGATOR and IPW BLU-285-1002 data. A: Expected time in the second-line health state in the ECM arm. B: Expected time in the third-line 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.
Each cycle, transition probability TP = Pr(prog) + Pr(death). $Pr(prog)_{2L,t}$ and $Pr(prog)_{3L,t}$ are the same in both arms every cycle and come from ECM 2L and 3L PFS censoring for death (where t: model cycle, 2L: second line, 3L: third line). $Pr(death)_{ECM,t}$ and $Pr(death)_{Avapritinib,t}$ are 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.

To summarize this approach, the model captures the value of avapritinib through its ability to increase PFS and OS compared with the ECM arm, without assuming that first-line avapritinib treatment slows down subsequent progression of disease. This approach implies a lack of second-line and third-line treatments in the ECM arm. This is because by assuming that progression rates are the same across arms, we also assume that progression of disease is not significantly slowed by current second-line and third-line therapies. This is based on the very low overall response rates to second-line sunitinib and third-line regorafenib (approximately 0–5%) seen in clinical practice among patients who have unresectable or metastatic *PDGFRA* D842V-mutated GIST.[16, 17, 67] In addition, responses to the clinical survey suggest

that in practice, these therapies have a lack of efficacy for patients who have unresectable or metastatic *PDGFRA* D842V-mutated GIST.[1]

The base-case imposes a structural assumption on the relative rate of progression in later lines for avapritinib patients. The uncertainty of this was explored by varying the relative risk of progression in the SoC1/second-line and SoC2/third-line health states. This relative risk is applied as a simple multiplier to the per-cycle progression probability for patients in the SoC1 and SoC2 health states. Results of the scenario analyses testing this assumption are presented in Section B.3.8.3.

This approach also assumes that aside from other modifying factors (e.g. AEs) unresectable or metastatic GIST patients at the same disease stage (i.e. first line, second line, third line, progressive disease in Figure 12) have the same health state utility and resource use regardless of their *PDGFRA* D842V mutational status. Given the lack of available HRQL or HCRU evidence specific to patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, this assumption cannot realistically be avoided.

Table 41 shows the modelled time in state and proportion of time alive in state, as simulated in the model base case. Despite the rate of progression of disease being constant across the treatment arms for the SoC1/second-line and SoC2/third-line health states, the proportion of expected time alive spent in first, second, and third line is higher in the avapritinib arm. This is due to the differences in first-line progression rate between the arms. The rate of progression from first-line therapy determines the inflow of patients into the SoC1/second-line and SoC2/third-line states. In other words, proportionately fewer avapritinib patients are progressing into SoC1 each cycle in the avapritinib arm than progressing into second line in the ECM arm. Consequently, avapritinib patients spend less time (proportionately) in worse disease states than ECM patients, even when the subsequent probability of progression in each model cycle is identical in both. This is reflective of the extension of PFS and OS indicated for avapritinib by the clinical evidence available (See Section B.2.6 and Section B.2.9).

Table 41: Expected time in each living state in the cost-effectiveness model – base case

Model state	Expected time in state (AVA arm), years	% of expected overall survival	Expected time in state (ECM arm), years	% of expected overall survival
AVA/IMA	[redacted]	[redacted]	[redacted]	[redacted]
SoC1/2L	[redacted]	[redacted]	[redacted]	[redacted]
SoC2/3L	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Total	10.38	100%	1.98	100%

Key: 1L, first line; 2L, second line; AVA, avapritinib; ECM; established clinical management; IMA, imatinib; SoC, standard of care; PD, progressed disease.

B.3.3.3.2. Established clinical management

First line

Figure 25 presents the visual fit of the parametric models to the IPW BLU-285-1002 data at first line. All models display similar visual fits to the Kaplan–Meier data during the follow-up period.

Figure 25: Progression-free survival models during trial follow-up – ECM, censoring for death, IPW-adjusted BLU-285-1002 at first-line

Key: ECM, established clinical management; IPW, inverse probability weighting; KM, Kaplan–Meier.

The survival estimates of each model over time are given in Figure 26 and Table 42. Again, each model presents similar extrapolations. Figure 27 shows the long-term hazard of progression or death for each model in a log cumulative hazard plot. Table 43 presents median and mean survival based on extrapolations of the IPW BLU-285-1002 data. This indicates a reducing hazard over time, as the mean is larger than the median in all cases.

Figure 26: Progression-free survival models extrapolated to 40 years – ECM, censoring for death, IPW-adjusted BLU-285-1002 at first-line

Key: ECM, established clinical management; IPW, inverse probability weighting; KM, Kaplan–Meier.

Figure 27: Progression-free survival log-cumulative hazard – ECM, censoring for death, IPW-adjusted BLU-285-1002 at first line

Key: ECM, established clinical management; IPW, inverse probability weighting; KM, Kaplan–Meier.

Table 42: Progression-free survival estimates at set time points – ECM, censoring for death, IPW-adjusted BLU-285-1002 at first line

Time	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0.0 years	[redacted]				
0.5 years					
1.0 years					
2.0 years					
5.0 years					
10.0 years					
20.0 years					
40.0 years					

Key: ECM, established clinical management; IPW, inverse probability weighting.

Table 43: Mean and median progression-free survival – ECM, censoring for death, IPW-adjusted BLU-285-1002 at first line

	Mean, years	Median, years
Kaplan–Meier	[redacted]	
Exponential		
Weibull		
Gompertz		
Log-normal		
Log-logistic		

Key: ECM, established clinical management; IPW, inverse probability weighting.

The statistical fit of each of the models to the BLU-285-1002 data was then considered with respect to the AIC and BIC values in Table 44. 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.

Table 44: Progression-free survival statistical fit – ECM, censoring for death, IPW BLU-285-1002 at first-line

Fit statistics	Akaike information criterion	Bayesian information criterion
Exponential	281.61	282.55
Weibull	279.67	281.56
Gompertz	360.63	362.52
Log-normal	361.54	363.43
Log-logistic	363.88	365.76
Key: ECM, established clinical management; IPW, inverse probability weighting.		

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. Given its closeness in AIC/BIC values and visual fit to the Weibull model, the exponential model was explored in a scenario analysis. Professors Ian Judson and Robin Jones confirmed that the resulting model generated reasonable clinical outcomes.

Second and third line

PFS data for patients on second- and third-line treatment in both arms are taken from IPW BLU-285-1002 data. In all lines the PFS analysis is censored for death events, meaning that the hazard estimated by parametric survival models only describes risk of progression. As discussed in Section B.3.2, the same rate per model cycle of progressing to the next treatment line has been conservatively assumed to apply to post-avapritinib patients in the base case (See Figure 24). A more detailed description of parametric model selection for patients on second- and third-line treatments is provided in Appendix O.2.[1]

B.3.3.4. Time on treatment

ToT for avapritinib was captured and extrapolated based on IPW NAVIGATOR data, using the 17 January 2020 data cut.

This analysis with and without IPW is presented in Figure 28. As can be seen, the weighting of the patient data does not make a considerable difference to the estimated time on treatment for the avapritinib arm.

Figure 28: Time on treatment Kaplan–Meier data – avapritinib: IPW adjusted versus unadjusted

Key: IPW, inverse probability weighting.
Notes: Analysis censors for death. Progression is an event.

Figure 29 shows the visual fit of all parametric models considered over the follow-up period for NAVIGATOR, while Figure 30 presents the models over 40 years. The absolute ToT values over time are given in Table 45. All models present reasonable fits to the observed data during the follow-up period.

Figure 29: Time on treatment models during trial follow-up – avapritinib, censoring for death, censoring for progression, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Figure 30: Time on treatment models extrapolated to 40 years – avapritinib, censoring for death, censoring for progression, IPW adjusted

Key: IPW, inverse probability weighting; KM, Kaplan–Meier.

Table 45: Time on treatment estimates at set time points – avapritinib, censoring for death, censoring for progression, IPW adjusted

Time	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0.0 years	[redacted]				
0.5 years					
1.0 years					
2.0 years					
5.0 years					
10.0 years					
20.0 years					
40.0 years					

Key: IPW, inverse probability weighting.

Table 46 was used as a basis to assess statistical fit. The exponential and Weibull models had the lowest AIC and BIC values, and these were within 5 of each other; therefore, these two models were considered to have the best statistical fit. However, the clinical expert consulted suggested that the model using Gompertz extrapolation of avapritinib ToT provided clinically plausible results. We consider this to overrule a decision made only based on statistical fit and therefore use Gompertz in the base case.

Table 46: Time on treatment statistical fit – avapritinib, censoring for death, censoring for progression, IPW adjusted

Fit statistics	Akaike information criterion	Bayesian information criterion
Exponential	134.20	136.22
Weibull	135.68	139.73
Gompertz	161.84	165.89
Log-normal	163.55	167.60
Log-logistic	162.81	166.86

Key: IPW, inverse probability weighting.

Furthermore, Professors Ian Judson and Robin Jones agreed that the resulting cost-effectiveness model estimates of OS and ToT were both clinically plausible.

B.3.3.5. Adverse events

AEs of treatments were included to account for the additional costs incurred due to treatment toxicities. Grade 3–4 AEs with incidence of greater than 2% in either treatment arm were considered.

If any reported AEs for the comparators were greater than 2% incidence, they were also included for avapritinib. 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.

B.3.3.5.1. Avapritinib

Table 47 summarizes all Grade ≥ 3 AEs with ≥ 2% incidence in the avapritinib arm full safety population. Table 48 presents the comparator AEs.

Table 47: NAVIGATOR adverse events, full safety population

Adverse event	Full safety pop (n = 237, follow-up = 10.8 months)	
	n	Cycle probability
Abdominal pain	[redacted]	[redacted]
Abnormal liver function results	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dermatitis/rash	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]

Adverse event	Full safety pop (n = 237, follow-up = 10.8 months)	
	n	Cycle probability
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

B.3.3.5.2. Established clinical management

The ECM arm consists of three different treatments, each with different safety profiles. These are considered while patients are present in the associated health state (imatinib, sunitinib or regorafenib).

AEs associated with imatinib treatment were sourced from a trial of patients with advanced GIST. These patients were randomly assigned to receive 400 mg or 600 mg of imatinib daily.[42] Patients could have received previous chemotherapeutic regimens, or have undergone radiotherapy or surgery. The study reported Grade 3–4 events that occurred in ≥ 5% of patients. AE data for patients treated with either the 400 mg or 600 mg dose were used in the model.

Data on the AEs of sunitinib were collected from an RCT for patients with advanced GIST after failure of imatinib.[43] Patients received a 50 mg starting dose of sunitinib daily for 4 weeks out of the 6-week treatment cycles. As available from the literature, Grade 3–4 events that occurred in ≥ 5% of patients were included in the model.

AE data for regorafenib were taken from a Phase III RCT for patients with advanced GIST after failure of imatinib and sunitinib.[45] Patients received regorafenib 160 mg daily (plus best supportive care) for the first 3 weeks of each 4-week cycle. Data for the Grade 3 AEs that occurred in ≥ 10% of patients as reported in the study were used in the model. Table 48 lists the comparator adverse events.

Table 48: Comparator adverse events

Adverse event	First line (n = 147, follow-up = 9.5 months)		Second line (n = 202, follow-up = 13.0 months)		Third line (n = 132, follow-up = 4.6 months)	
	n	Cycle probability	n	Cycle probability	n	Cycle probability
Abdominal pain	1	0.00072		0.00000		0.00000
Abnormal liver function results	4	0.00288		0.00000		0.00000
Anaemia	3	0.00216	7	0.00266		0.00000
Ascites		0.00000		0.00000		0.00000
Asthenia		0.00000	6	0.00228		0.00000
Blood bilirubin increased		0.00000		0.00000		0.00000
Confusional state		0.00000		0.00000		0.00000
Decreased appetite		0.00000		0.00000		0.00000
Diarrhoea	3	0.00216	7	0.00266	7	0.01142
Dermatitis/Rash	4	0.00288		0.00000	29	0.04729
Dyspnoea		0.00000		0.00000		0.00000
Fatigue		0.00000	10	0.00380	3	0.00489
Oedema	2	0.00144		0.00000		0.00000
Haemorrhage	7	0.00503		0.00000		0.00000
Hypertension		0.00000	6	0.00228	30	0.04892
Hypokalaemia		0.00000		0.00000		0.00000
Hyponatraemia		0.00000		0.00000		0.00000
Hypophosphataemia		0.00000		0.00000		0.00000
Leukopenia	2	0.00144	7	0.00266		0.00000
Lymphopenia		0.00000	19	0.00721		0.00000
Nausea	2	0.00144		0.00000		0.00000
Neutropenia	7	0.00503	20	0.00759		0.00000
Neutrophil count decreased		0.00000		0.00000		0.00000

Adverse event	First line (n = 147, follow-up = 9.5 months)		Second line (n = 202, follow-up = 13.0 months)		Third line (n = 132, follow-up = 4.6 months)	
	n	Cycle probability	n	Cycle probability	n	Cycle probability
Pleural effusion		0.00000		0.00000		0.00000
Pneumonia		0.00000		0.00000		0.00000
Sepsis		0.00000		0.00000		0.00000
Vomiting	1	0.00072		0.00000		0.00000
Notes: First line is proxied by imatinib, second line is proxied by sunitinib, and third line is proxied by regorafenib.						

B.3.4. Measurement and valuation of health effects

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

HRQL data were not collected in the NAVIGATOR trial. Furthermore, to our knowledge, no EQ-5D-based or EQ-5D-mappable evidence on HRQL specific to patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST exists.

B.3.4.2. Mapping

No evidence relating to the HRQL for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST was identified. Therefore, no mapping was necessary or possible.

B.3.4.3. Health-related quality-of-life studies

Appendix H summarizes the SLR process. No studies specific to patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST or usable data from related disease areas were found.

B.3.4.4. Adverse reactions

The impact of Grade 3–4 AEs has been explored in the cost-effectiveness analysis. Utility decrements for each of the AEs included in the analysis (described in Section B.3.3) were sourced from a targeted review of the literature or used in previous appraisals. When an appropriate utility decrement estimate could not be sourced, the maximum of the available utility decrements was assumed.

A duration of 7 days was applied to disutilities, in line with the approach used in TA176 and TA240 (TA439 provides review documents relating to these submissions) where expert opinion from Freeman et al. indicated durations of a maximum of 7 days for Grade 3–4 AEs.[68] As in TA176 and TA240, it was assumed that although some AEs may persist for longer than 7 days, this is likely to be with reduced severity. Grade 1–2 AEs are assumed to have no disutility.

Table 49 summarizes the AE utility decrements and sources used in the cost-effectiveness analysis.

Table 49: Adverse event utility decrements and durations

Adverse event	Disutility	Source
Abdominal pain	0.069	Doyle et al. (2008)[69] [TA176/TA240]
Abnormal liver function results	0.200	Assume the maximum of the available utility decrements
Anaemia	0.085	Harrow et al. (2011)[70] [TA176/TA240]
Ascites	0.200	Assume the maximum of the available utility decrements
Asthenia	0.115	Assume equal to disutility for fatigue
Blood bilirubin increased	0.200	Assume the maximum of the available utility decrements
Confusional state	0.200	Assume the maximum of the available utility decrements
Decreased appetite	0.158	Freeman et al. (2015),[71] assumed anorexia
Diarrhoea	0.103	Lloyd et al. (2006)[72] [TA176/TA240]
Dermatitis/rash	0.032	Nafees et al. (2008)[73] [TA176/TA240]
Dyspnoea	0.200	Assume the maximum of the available utility decrements
Fatigue	0.115	Lloyd et al. (2006)[72] [TA176/TA240]
Oedema	0.060	Freeman et al. (2015)[71] [Table 112]
Haemorrhage	0.200	Assume the maximum of the available utility decrements
Hypertension	0.069	Doyle et al. (2008)[69] [TA176/TA240]
Hypokalaemia	0.115	Assume equal to disutility for fatigue
Hyponatraemia	0.090	Assume equal to disutility for neutropenia
Hypophosphataemia	0.090	Assume equal to disutility for neutropenia
Leukopenia	0.090	Assume equal to disutility for neutropenia
Lymphopenia	0.090	Assume equal to disutility for neutropenia
Nausea	0.048	Nafees et al. (2008)[73]
Neutropenia	0.090	Nafees et al. (2008)[73] [TA176/TA240]
Neutrophil count decreased	0.090	Assume equal to disutility for neutropenia
Pleural effusion	0.200	Assume the maximum of the available utility decrements
Pneumonia	0.200	Freeman et al. (2015)[71] [Table 110]
Sepsis	0.195	Freeman et al. (2015)[71] [Table 106]
Vomiting	0.103	Lloyd et al. (2006)[72] [TA176/TA240]

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

Given the absence of evidence in unresectable or metastatic *PDGFRA* D842V-mutated GIST, health-state utility values from previous unresectable or metastatic

GIST TAs (TA86, TA179, and TA488)[1] have been used to capture the HRQL of unresectable or metastatic *PDGFRA* D842V-mutated GIST patients as they move through the treatment pathway.

Table 50 describes the health-state utility values and the sources they are taken from. Note that some of the health-state utility values provided within TA86, TA179, or TA488 are superseded by the more recent submissions. A post-progression disease value of 0.577 was provided in TA179, which is considerably lower than the post-progression value in TA488. However, since TA179, TA488 has replaced the next steps in the treatment pathway, meaning that those patients for whom second-line therapy fails are now treated with third-line therapy before entering the progressive disease health state. For this reason, in the base case the higher value from TA488 (0.647) is used. A scenario using a value of 0.577 is included in the scenario analysis to test the impact of this structural assumption on the results, and to explore the impact of the worsening of the PD state on the results.

In a clinical survey, 5/5 (100%) clinicians agreed that the utility values shown in Table 50 are likely to be reflective of the HRQL of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in current UK clinical practice.[1] Furthermore, 5/5 (100%) agreed that these utility values were also likely to be reflective of patients in UK clinical practice following the introduction of avapritinib, excluding modifying factors such as AEs.[1]

Table 50: Summary of utility values for cost-effectiveness analysis

	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Health state			
AVA/1L	0.935 (0.094)	Section B.3.4.5, page 120	No other evidence available, clinical experts suggest similar burden
SoC1/2L	0.781 (0.078)	Section B.3.4.5, page 120	
SoC2/3L	0.767 (0.077)	Section B.3.4.5, page 120	
PD	0.647 (0.065)	Section B.3.4.5, page 120	

	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Adverse event			
Abdominal pain	-0.069	Section B.3.4.4, p119	Identified through targeted published literature search or assumed equivalent to published estimate for a similar adverse event
Abnormal liver function results	-0.200		
Anaemia	-0.085		
Ascites	-0.200		
Asthenia	-0.115		
Blood bilirubin increased	-0.200		
Confusional state	-0.200		
Decreased appetite	-0.158		
Diarrhoea	-0.103		
Dermatitis/Rash	-0.032		
Dyspnoea	-0.200		
Fatigue	-0.115		
Oedema	-0.060		
Haemorrhage	-0.200		
Hypertension	-0.069		
Hypokalaemia	-0.115		
Hyponatraemia	-0.090		
Hypophosphataemia	-0.090		
Leukopenia	-0.090		
Lymphopenia	-0.090		
Nausea	-0.048		
Neutropenia	-0.090		
Neutrophil count decreased	-0.090		
Pleural effusion	-0.200		
Pneumonia	-0.200		
Sepsis	-0.195		
Vomiting	-0.103		
Key: 1L, first line; 2L, second line; 3L, third line; AVA, avapritinib; PD, progressive disease; SoC, standard of care; TA, technology appraisal.			

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. This was done by estimating the utility values of the general population at each age and creating a utility multiplier based upon the algorithm by Ara and Brazier (2010).[74] This multiplier

is applied in each cycle throughout the model time horizon. The algorithm used to estimate the multiplier is shown below:

*General population utility value = 0.9508566 + 0.0212126*male – 0.0002587*age – 0.0000332*age^2*

The general population baseline age is estimated from the same starting age and proportion of males of the model (see Table 7).

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In line with the NICE reference case, the perspective on costs in all cost-effectiveness analyses is that of the NHS and Personal Social Services (PSS) in England. An SLR for HCRU and cost data relevant to this submission is reported in Appendix I.

B.3.5.1. Intervention and comparators' costs and resource use

Acquisition costs associated with the intervention and comparators are presented below. List prices were sourced from the Monthly Index of Medical Specialities. For each oral therapy, the pack cost for the most efficient tablet dose in line with the recommended doses in Section B.3.5 was used to inform acquisition costs.

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

B.3.5.1.1. Avapritinib treatment cost

The licensed dose for avapritinib is expected to be 300 mg/day, so the price of a bottle of 300 mg tablets was used (Table 51). All possible doses of avapritinib will have the same effective cost, meaning that the dose that a patient receives will have no bearing on the cost of treating that patient.

During uninterrupted treatment of avapritinib at any possible dose, one bottle of avapritinib tablets will last for 30 days. However, analysis of the NAVIGATOR data suggests that NAVIGATOR patients on average spend some of their time on avapritinib treatment on a treatment break. As a result, the true duration that one

bottle of tablets lasts is longer than 30 days. We take this into account in the form of a multiplier on the monthly cost of treating patients.

For simplicity within the cost-effectiveness model, the proportion of NAVIGATOR patients not on a dose break was used as a multiplier to the cost of avapritinib. This is a conservative approach considering that dose reductions also effectively reduce the cost of treating a patient because each bottle of tablets will last longer as a result. The mean relative dose intensity of [redacted] was obtained from NAVIGATOR. This was applied when calculating an average cost per cycle for avapritinib.

Finally, the study protocol for NAVIGATOR describes cautionary suspension of treatment for any Grade 2+ incidents of cognitive effects or intracranial bleeding. These suspensions are reflected in the relative dose intensity applied within the model (See Table 32). However, we believe that in practice any incidents of these two events would lead to a 14-day treatment suspension. Consequently, a 14-day treatment suspension was assumed within the model following the occurrence of either event at Grade 1. The probability of this event per (1-month) model cycle according to NAVIGATOR data is 0.025, meaning that a further multiplier of 98.8% is applied to the final per-cycle cost of avapritinib treatment.

Table 51: Cost of avapritinib

Dose	Number of capsules per bottle	Price per bottle	Source
100 mg	30	£26,666.67 (PAS price: £[redacted])	Blueprint
200 mg	30	£26,666.67 (PAS price: £[redacted])	Blueprint
300 mg	30	£26,666.67 (PAS price: £[redacted])	Blueprint

B.3.5.1.2. Imatinib treatment cost

The recommended dose for imatinib is 400 mg per day. Imatinib was therefore costed according to the price of a pack of 400 mg tablets (see Table 52). Although imatinib is available as a generic medicine, the EMA has not approved it to treat patients who have GIST. The branded pack price of imatinib has therefore been used in the model.

We assumed that there are no dose reductions or escalations for imatinib patients, following from the final appraisal determinations from NICE TA86 and TA209, which provided a negative determination for imatinib dose changes.[29, 54]

Table 52: Cost of imatinib

Dose	Number of capsules per pack	Price per pack	Source
400 mg	30	£1,133.41	Monthly Index of Medical Specialties[75]

B.3.5.1.3. Sunitinib treatment cost

The recommended dose for sunitinib is 50 mg daily for 4 weeks, followed by a 2-week treatment-free interval in each 6-week cycle. Sunitinib was therefore costed according to the price of a pack of 50 mg tablets (see Table 53). A 97% relative dose intensity is used for sunitinib based on TA179.

Table 53: Cost of sunitinib

Dose	Number of capsules per pack	Price per pack	Source
50 mg	28	£3,138.80	Monthly Index of Medical Specialties[76]

B.3.5.1.4. Regorafenib treatment cost

The pack price of regorafenib applied in the model is given in Table 54. An 87% relative dose intensity is used for regorafenib based on TA488.

Table 54: Cost of regorafenib

Dose	Number of capsules per pack	Price per pack	Source
40 mg	84	£3,744.00	Monthly Index of Medical Specialties[77]

Costs per treatment administration were calculated for each treatment. The monthly cost of each treatment was then determined based on the cost per administration, average administrations per model cycle and relative dose intensities (Table 55).

Table 55: Treatment cost per cycle

Treatment	Cost per administration	Cost per model cycle
Avapritinib	£888.89 (list price)	£23,332.55 (list price)
Imatinib	£37.78	£1,149.94
Sunitinib	£112.10	£2,206.45
Regorafenib	£178.29	£3,540.84

As discussed in Section B.3.3, total drug costs are derived by applying the treatment costs per cycle to the duration of treatment (where available) or PFS to estimate the proportion of patients on treatment per model cycle, or a combination of the two.

B.3.5.2. Health-state unit costs and resource use

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. Furthermore, very little information on this is available in the literature or previous NICE submissions (TA86 and TA179).[29, 44] The TA179 submission dossier, for example, was developed in 2008 and contains no additional resource use categories not already captured within the more recent TA488 dossier. Therefore, the HCRU cost values from the most recent GIST technology appraisal, TA488, were used for this analysis and inflated to 2018–2019 prices using the Personal Social Services Research Unit index.

The resource use frequencies in TA488 were based on a survey conducted in 2013 involving 15 physicians from England and Wales. These frequencies were revalidated in 2016 by two consultant oncologists based on the clinical practice in England at the time of the submission.

Table 56 gives the one-off costs of tests taken by a proportion of patients before treatment in addition to palliative surgical resection and palliative radiotherapy given to relieve or prevent symptoms. Regular resource use per patient, including pain management, is reported in Table 57.

A recent clinical survey provided some estimates of resource use, and these are included in a scenario analysis (Appendix R).[1]

Table 56: One-off resource use

Resource	Unit cost	Progression-free		Progressed		Source
		% patients	One-off cost	% patients	One-off cost	
CT scan	£115.19	85%	£97.91	–	–	NICE TA488; NHS reference costs 18/19 (three Areas, with contrast, RD26Z)[58]
MRI scan	£142.76	12%	£17.13	–	–	NICE TA488; NHS reference costs 18/19 (weighted average of MRI codes RD01A to RD07Z)[58]
Full blood count	£2.79	92%	£2.56	–	–	NICE TA488; NHS reference costs 18/19 (haematology DAPS05)[58]
Liver function test	£1.10	92%	£1.01	–	–	NICE TA488; NHS reference costs 18/19 (clinical biochemistry DAPS04) [58]
Palliative intervention						
Palliative resection	£4,199.27	10%	£419.93	10%	£419.93	NICE TA488 (progressed assumed to be same as PFS); NHS reference costs 18/19 (weighted average of costs of single intervention for malignant GI tract disorder: FD11D, FD11E, FD11F) [58]
Palliative radiotherapy	£182.71	20%	£36.54	20%	£36.54	NICE TA488 (progressed assumed to be same as PFS); NHS reference costs 18/19 (weighted average of adult medical specialist palliative care attendance costs: SD01A, SD02A, SD03A, SD04A) [58]
Total			**£575.08**		**£456.47**	

Key: CT, computed tomography; GI, gastrointestinal tract; MRI, magnetic resonance imaging; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; TA, technology appraisal.

Table 57: Regular resource use

Resource	Unit cost	Progression-free			Progressed			Source
		Monthly use	% patients	Per cycle cost	Monthly use	% patients	Per cycle cost	
Monitoring and tests								
CT scan	£115.19	0.36	100%	£41.39	0.30	100%	£34.54	NICE TA488; NHS reference costs 18/19 (three Areas, with contrast, RD26Z) [58]
MRI scan	£142.76	0.22	100%	£31.19	0.54	100%	£77.59	NICE TA488; NHS reference costs 18/19 (weighted average of MRI codes RD01A to RD07Z) [58]
Full blood count	£2.79	0.68	100%	£1.89	0.49	100%	£1.38	NICE TA488; NHS reference costs 18/19 (haematology DAPS05) [58]
Liver function test	£1.10	0.68	100%	£0.75	0.46	100%	£0.51	NICE TA488; NHS reference costs 18/19 (clinical biochemistry DAPS04) [58]
Outpatient care visit	£190.64	0.70	100%	£133.70	0.63	100%	£120.14	NICE TA488 (freq. from patients on BSC); NHS reference costs 18/19 (WF01A) [58]

Resource	Unit cost	Progression-free			Progressed			Source
		Monthly use	% patients	Per cycle cost	Monthly use	% patients	Per cycle cost	
Pain management								
Co-codamol 8/500	£0.01	243.5	18%	£0.36	243.5	22%	£0.44	NICE TA488; eMIT (8 tablets/day) [58]
Tramadol 50 mg	£0.01	243.5	12%	£0.27	243.5	14%	£0.32	NICE TA488; eMIT (8 tablets/day) [58]
Paracetamol 500 mg	£0.00	243.5	33%	£0.31	243.5	38%	£0.36	NICE TA488; eMIT (8 tablets/day) [58]
Morphine sulphate 10 mg	£0.06	547.9	20%	£6.34	547.9	29%	£9.19	NICE TA488; MIMS (18 tablets/day) [58]
Dexamethasone 2 mg	£0.25	60.9	11%	£1.65	60.9	19%	£2.85	NICE TA488; eMIT (2 tablets/day) [58]
Total				**£217.86**			**£247.32**	

Key: BSC, best supportive care; CT, computed tomography; eMIT, UK drugs and pharmaceutical electronic market information tool; GI, gastrointestinal tract; MIMS, Monthly Index of Medical Specialties; MRI, magnetic resonance imaging; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; TA, technology appraisal.

In the model, one-off resource use costs associated with first-line treatment are applied in the first cycle. One-off resource use costs associated with subsequent lines disease are applied to the proportion of patients transitioning to the progressed disease health state per model cycle. Regular resource use costs are multiplied by the proportion of patients in respective lines of treatment per cycle. Resource use is modelled consistently across both the avapritinib and comparator treatment arms.

B.3.5.3. Adverse reaction unit costs and resource use

Both avapritinib and the comparator therapies can incur serious adverse reactions. Table 58 below details the cost of resolving each AE included in the model.

Table 58: Cost of resolution of adverse events for this cost effectiveness analysis

Adverse event	Cost of resolution (£)	Source(s)
Abdominal pain	£634.50	NHS reference costs 2018/19 (assumed weighted average of FD05A:FD05B)[78]
Abnormal liver function results	£520.62	NHS reference costs 2018/19 (assumed weighted average of WH13A:WH13C) [78]
Anaemia	£752.06	NHS reference costs 2018/19 (assumed weighted average of SA01G:SA01K, SA03G:SA03H, SA04H:SA04L and SA05G:SA05J) [78]
Ascites	£5,265.99	NHS reference costs 2018/19 (assumed weighted average of YF03A:YF03B and YF04A:YF04C) [78]
Asthenia	£595.53	Assume equal to fatigue (TA581, TA580)
Blood bilirubin increased	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J) [78]
Confusional state	£2,254.99	NHS reference costs 2018/19 (assumed WD01Z, total HRGs) [78]
Decreased appetite	£589.07	NHS reference costs 2018/19 (Non-elective short stay, in line with TA581) [78]
Diarrhoea	£1,148.47	NHS reference costs 2018/19 - FD10F (Non elective short stay; in line with TA581) [78]
Dermatitis/Rash	£589.07	NHS reference costs 2018/19 (Non-elective short stay, in line with TA581) [78]
Dyspnoea	£619.56	NHS reference costs 2018/19 (assumed weighted average of DZ19H:DZ19N) [78]
Fatigue	£595.53	NHS reference costs 2018/19 (Non-elective short stay) plus cost of nurse visit (in line with TA581) [78]

Adverse event	Cost of resolution (£)	Source(s)
Oedema	£575.99	NHS reference costs 2018/19 (assumed weighted average of WH10A:WH10B) [78]
Haemorrhage	£1,204.58	NHS reference costs 2018/19 (assumed weighted average of FZ38G:FZ38P) [78]
Hypertension	£598.58	NHS reference costs 2018/19 - EB04Z - Total HRGs[78]
Hypokalaemia	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J) [78]
Hyponatraemia	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J) [78]
Hypophosphataemia	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J) [78]
Leukopenia	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J) [78]
Lymphopenia	£1,033.43	NHS reference costs 2018/19 (assumed weighted average of SA08G:SA08J)
Nausea	£1,148.47	NHS reference costs 2018/19 - FD10F (Non elective short stay; in line with TA581) [78]
Neutropenia	£2,103.72	NHS reference costs 2018/19 - SA08J - (Non elective long stay; in line with TA604) [78]
Neutrophil count decreased	£2,103.72	Assumed same as neutropenia
Pleural effusion	£1,684.01	NHS reference costs 2018/19 (assumed weighted average of DZ16H:DZ16R) [78]
Pneumonia	£2,701.77	NHS reference costs 2018/19 - weighted average of DZ11K:DZ11V (Non elective long stay; in line with TA604) [78]
Sepsis	£2,205.65	NHS reference costs 2018/19 (assumed weighted average of WJ06A:WJ06J) [78]
Vomiting	£1,148.47	NHS reference costs 2019/19 - FD10F (Non elective short stay; in line with TA581) [78]
Key: NHS, National Health Service.		

For each model cycle, the cost of each AE was multiplied by its probability per cycle and the proportion of patients on treatment. The probability per cycle of each AE per treatment is given in Section B.3.3.

B.3.5.4. Miscellaneous unit costs and resource use

As the model has effectively a lifetime time horizon, the introduction of end-of-life costs does not affect the undiscounted model outcomes. This is because all patients

have died in both arms by the time horizon, so the total undiscounted cost associated with end-of-life care is identical in each arm. However, the cost associated with end-of-life care is relevant to discounted model outcomes when mortality differs between arms, since a larger proportion of end-of-life costs are incurred later in the arm with lower mortality. To capture this, end-of-life costs were incorporated into the cost-effectiveness model.

End-of-life costs were taken from NICE TA488 and inflated to 2018/19 prices using indices from the Personal Social Services Research Unit (PSSRU).[58] The original cost is taken from a study conducted by Abel et al. that presents end-of-life costs for a cohort of hospice patients in South West England.[79] The resulting cost of £9,144.20 in Table 59 was allocated for each patient upon death. In line with advice from NICE, a scenario is included using estimates from Round et al.[80]

Table 59: End-of-life cost

Detail on end-of-life	% of patients	Cost
Death in hospital	16%	£11,299
Death outside of hospital	84%	£7,730
Weighted total (inflated to 2018/2019)		**£9,144.20**

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base case analysis inputs

A summary of all base case parameters and distributions are provided in Appendix M.

B.3.6.2. Assumptions

A table of modelling assumptions is provided below, in Table 60. This is divided by aspect of the cost-effectiveness model.

Table 60: Assumptions table

Assumption	Justification
Clinical parameters and variables	
When a patient stops treatment with avapritinib, the benefit of avapritinib in terms of mortality is lost gradually.	• Clinical experts have suggested that the treatment effect is not lost immediately when a patient is discontinued from avapritinib and may continue for 60 months[53, 55] • With no further information on the dynamics of the loss of this effect over time, linear interpolation was used
Once a patient has lost the avapritinib treatment effect, it is appropriate to model their survival based on the ECM arm.	• We propose that once the treatment effect is completely lost, no further survival benefit should be modelled • Clinical experts confirmed in a survey that the overall survival of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST does not significantly differ as a result of treatment with imatinib, sunitinib, regorafenib or best supportive care
The rate of further disease progression in patients with progressed disease in the avapritinib and ECM arms is the same.	• Clinical experts confirmed in a survey that the overall survival of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST does not significantly differ as a result of treatment with imatinib, sunitinib, regorafenib or best supportive care
Health-related quality of life	
Health-state utility values from previous GIST appraisals are appropriate for decision making in this indication.	• No data are available to capture the specific HRQL of patients with this mutation • 100% of clinical experts consulted suggested that these values are representative • The progressive disease health-state utility value from TA179 was explored in a scenario analysis.
Cost and health care resource use	
Excluding the management of adverse events and TKIs, the cost of treating patients with metastatic or	• Excluding adverse events, there is no evidence to suggest that disease management costs will differ

Assumption	Justification
unresectable *PDGFRA* D842V-mutated GIST is the same as treating patients with general GIST.	
The use of branded pack costs for imatinib is appropriate.	• Generic imatinib is not currently approved by the EMA for use in GIST treatment. See Section B.3.5.1
The first-line, second-line and third-line TKIs used in the treatment of patients with unresectable or metastatic GIST cost the equivalent to imatinib, sunitinib and regorafenib, respectively.	• In a survey of clinical experts, the majority of participants confirmed that, excluding patients who receive experimental therapies via clinical trials, compassionate use programmes or other means, patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in England and Wales are treated with imatinib, sunitinib and regorafenib, with most indicating that these would be used as first-, second- and third-line therapies, respectively, despite the lack of efficacy of these treatments • The mix of first-line therapies received by patients in IPW-adjusted BLU-285-1002 was explored in a scenario analysis
Key: ECM, established clinical management; GIST, gastrointestinal stromal tumour; HRQL, health-related quality of life; IPW, inverse probability weighting; *PDGFRA*, platelet-derived growth factor receptor alpha; TA, technology appraisal; TKI, tyrosine kinase inhibitor.	

B.3.7. Base case results

B.3.7.1. Base case incremental cost-effectiveness analysis results

Table 61 presents the base case incremental cost-effectiveness results for avapritinib at the proposed patient access scheme (PAS) price. Avapritinib is shown to be cost effective versus ECM at a £50,000 willingness-to-pay (WTP) threshold.

Table 61: Base case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
ECM	[redacted]	1.77	[redacted]				
Avapritinib	[redacted]	8.01	[redacted]	[redacted]	6.24	[redacted]	49,996
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 62: Base case results (undiscounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
ECM	[redacted]	1.98	[redacted]				
Avapritinib	[redacted]	10.38	[redacted]	[redacted]	8.40	[redacted]	41,570
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed within the cost-effectiveness model for 1,000 iterations. The visual results of the probabilistic sensitivity analysis runs are displayed in Figure 31 and Figure 32.

The results of the probabilistic analysis are similar to those of the deterministic analysis. At a WTP threshold of £50,000/QALY, avapritinib has a 42.4% chance of being cost effective.

Table 63: Sensitivity analysis results comparison (discounted, with PAS)

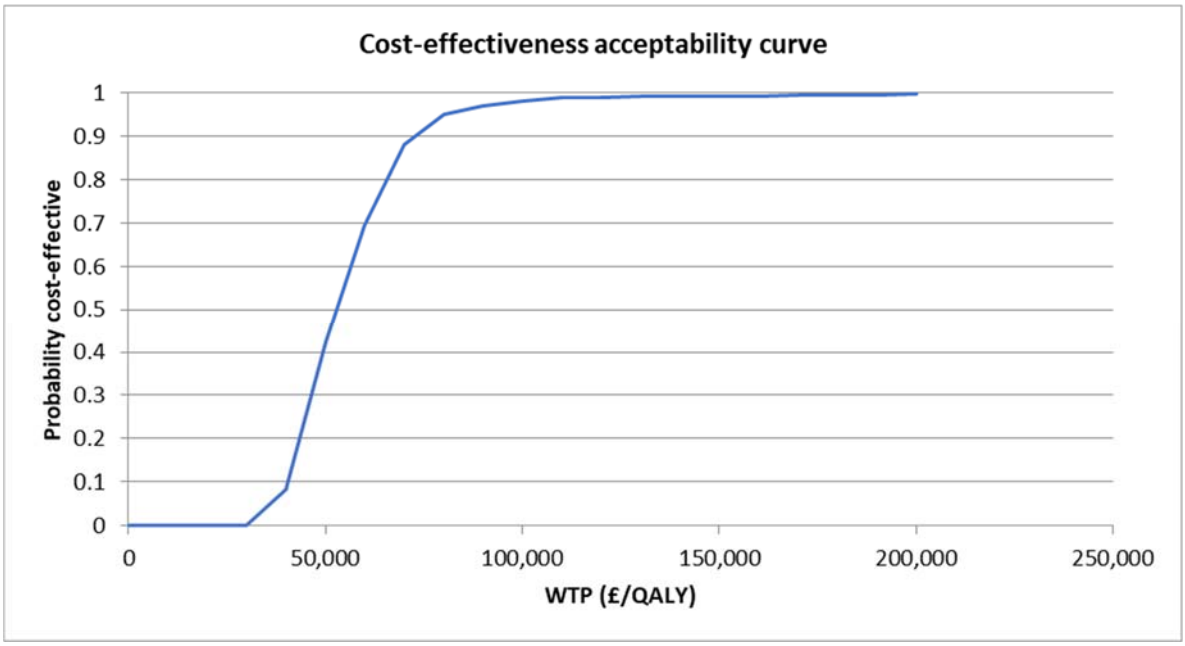
Technology	Total costs (£)		Total QALYs		ICER (£/QALY)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
ECM	[redacted]	[redacted]	[redacted]	[redacted]		
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	52,375	49,996

Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 31: Cost-effectiveness plane (1,000 probabilistic sensitivity analysis runs; discounted, with PAS)

Key: CE, cost-effectiveness; QALY, quality-adjusted life year.

Figure 32: Cost-effectiveness acceptability curve – Avapritinib (discounted; with PAS)



Key: QALY, quality-adjusted life year; WTP, willingness to pay.

B.3.8.2. Deterministic sensitivity analysis

Figure 33 presents the tornado diagram showing the parameters with the greatest impact on the results with descending sensitivity from one-way sensitivity analysis, when their values were set to their upper and lower limits of the confidence intervals reported in Appendix M.

The parameters that had the largest impact on the ICER for avapritinib versus ECM were baseline patient age, the annual discount rates and health state utility values.

Figure 33: Tornado diagram showing one-way sensitivity analysis results on ICER

Key: 1L, first-line; 2L, second-line; 3L, third-line; ICER, incremental cost effectiveness ratio; PD, progressed disease; PF, progression-free; QoL, quality of life.

B.3.8.3. Scenario analysis

Table 64: Scenario analysis results

Scenario	ICER
Base case	£49,996
No discounting	£41,570
No discounting: Outcomes	
No discounting: Costs	
Time horizon: 6 years	
Time horizon: 10 years	
ECM TKIs from Study 1002	
Incomplete loss of treatment benefit: 10%	
Incomplete loss of treatment benefit: 20%	
Post-ava progression rate slower: 10%	
Post-ava progression rate slower: 20%	
EoL costs from Round et al.	
PD utility from Sunitinib TA	

Scenario	ICER
Palliative surgery, radiotherapy, hospitalizations from clinical Survey	[redacted]
Cassier et al. survival for comparator arm	[redacted]
Overall survival: Avapritinib - log-logistic	[redacted]
Progression-free survival: Avapritinib - exponential	[redacted]
Progression-free survival: ECM - exponential	[redacted]
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PD, progressive disease; TA, technology appraisal; TKI, tyrosine kinase inhibitor;	

B.3.8.4. Summary of sensitivity analyses results

The results of the probabilistic sensitivity analysis are comparable to those of the deterministic analysis, with the influence of varying asymmetric distributions (i.e. survival, utilities) causing some minor deviation on the survival and HRQL side. The cloud is centred on an ICER of approximately £50,000, giving a cost-effectiveness acceptability curve result of 42.4%. This emphasizes the large amount of uncertainty surrounding the cost-effectiveness model results. In addition, the tornado diagram in Figure 33 shows the importance of parameters for which little evidence is available, such as health state utility values. Finally, the deterministic scenario analysis highlights the impact of efficacy assumptions. In practice, avapritinib will be used as a first-line therapy, and the data from NAVIGATOR are from a mixture of patients at different lines. The base case efficacy is then likely underestimated, though we do not yet know by how much. In conclusion, the analysis of uncertainty supports the case for an ICER of approximately £50,000, which is considered to be cost effective in the UK inside of the end-of-life criteria.

B.3.9. Subgroup analysis

In line with the final scope, no subgroups were modelled within the economic evaluation.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

Clinical validation was carried out on the below categories, which are summarized here:

- The survival estimates produced by the cost-effectiveness model
- Health-state utility values
- The current and avapritinib treatment pathways
- HCRU

B.3.10.1.1. Survival estimates

The survival estimates produced by the final base case model were presented to two clinical experts independently. In both cases, the clinical experts indicated that the PFS and OS estimates produced by the model are clinically plausible, given the disease-modifying effect of avapritinib for eligible patients.

B.3.10.1.2. Health state utility values

During a clinical survey, to which five clinical experts responded, 100% supported the health state utility values used in our base case. However, some structural uncertainty remains regarding the utility associated with the progressive disease health state. Therefore, we include a scenario which applies the post-progression utility used in the NICE submission for sunitinib in unresectable or metastatic GIST.[44] This did not considerably affect the model results (See Table 64).

B.3.10.1.3. Treatment pathways

In a survey of clinical experts, the majority of participants confirmed that, excluding patients who receive experimental therapies via clinical trials, compassionate use programmes or other means, patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in England and Wales are treated with imatinib, sunitinib and regorafenib, with most indicating that these would be used as first-, second- and third-line therapies, respectively, despite the lack of efficacy of these treatments.

However, as there was not a complete consensus on this point, some structural uncertainty remains. We therefore include a scenario analysis using the only other

available evidence on this, the BLU-285-1002 study (See Appendix Q). This does not considerably impact the ICER, increasing it by less than £1,000 (See Table 64)

B.3.10.1.4. Healthcare resource use

Clinical opinion on HCRU at different treatment lines was mixed, with a lack of a clear consensus when evaluating the responses from our clinician survey. As this suggested that the HCRU information provided by the experts may not be 100% reliable, we used values from previous NICE TAs in unresectable or metastatic GIST in our base case. However, this constitutes structural uncertainty, so we introduced a scenario applying the values suggested by the clinical survey results (Appendix R). This has a reasonable impact on the ICER (around £6,000), and so remains an area of uncertainty which could be addressed going forward.

B.3.11. Interpretation and conclusions of economic evidence

B.3.11.1. Overview

For patients receiving ECM for unresectable or metastatic *PDGFRA* D842V GIST in the UK, the OS and PFS expectation is very poor due to the lack of efficacy of the currently available TKI treatments. Clinical experts have emphasized a clear unmet need in this patient population. The clinical evidence available clearly demonstrates that median OS is under 2 years, while PFS is expected to be only 3 months. With median survival in the NAVIGATOR trial [redacted] ([redacted] months beyond the median survival in the IPW BLU-285-1002 analysis), the clinical evidence clearly supports the notion that avapritinib meets the criteria as an life-extending end-of-life therapy and that the cost-effectiveness threshold of interest is therefore £50,000.

Driven by results from the NAVIGATOR 17 January 2020 interim data cut and IPW BLU-285-1002 data, the cost-effectiveness model estimates an expected OS benefit of [redacted] years, along with a first-line PFS benefit of [redacted]. This estimated PFS benefit is in fact greater than the current expectation of OS in the ECM population. This magnitude of benefit is in line with clinical expectations, as leading experts in the field have confirmed that the survival results are clinically plausible. Avapritinib therefore represents a step change in the treatment of these end-of-life patients, who currently have a clear unmet need.

The NAVIGATOR trial data derives from patients at various lines of therapy, though the expectation is that in clinical practice, avapritinib will be used as a first-line treatment for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST, and much of the benefit will manifest as long-term survival. Consequently, the clinical evidence available likely provides a conservative estimate of long-term OS, and potentially gives a conservative estimate of the absolute OS benefit conferred by avapritinib. Thus, the results of the cost-effectiveness analysis may be somewhat conservative.

The uncertainty surrounding long-term survival benefit will naturally resolve itself over time as the NAVIGATOR cohort matures, potentially supported by evidence from VOYAGER when this becomes available. This survival uncertainty has a large impact on our cost-effectiveness estimates. Therefore, Blueprint Medicines is seeking a recommendation for avapritinib for use within the Cancer Drugs Fund (CDF) in the UK. This would enable access to a highly effective medicine while allowing the data to mature, which would alleviate the primary source of uncertainty in the current evidence base, enabling an informed final decision on the use of avapritinib in this indication.

Our base case cost-effectiveness results suggest that avapritinib is cost effective at a WTP of £50,000 per QALY. The base case ICER of £49,996 at a PAS discount of [redacted] falls within the appropriate cost-effectiveness threshold, and many of the scenario analysis results provide an ICER below our base case. As such, avapritinib has been demonstrated to be a cost-effective use of NHS resources.

B.3.11.2. Strengths and limitations of the analysis

B.3.11.2.1. Strengths

One of the main strengths of our analysis is that we have linked survival outcomes in our cost-effectiveness model. This means that any changes to ToT or PFS have an associated impact on OS. As there is no evidence on PFS at later lines of treatment, this enabled us to make conservative base case assumptions about the ability of avapritinib to slow down subsequent progression of disease beyond discontinuation. This added flexibility and adaptability of the modelling framework allows many

scenarios to be explored, and enables us to model the entire treatment pathway, rather than forgo important detail within the post-progression health state.

Our model explicitly models treatment waning, which occurs gradually – in line with advice from clinical experts. This allows us to capture the clinical expectation of treatment efficacy, using all of the available evidence and expert clinical opinion

Our IPW analysis allows us to make use of the most recent and richest available data set of patients with unresectable or metastatic *PDGFRA* D842 GIST not treated with avapritinib, without making a naïve comparison. We have included all of the prognostic variables included in BLU-285-1002 for which there were sufficient data. We believe that with current available data, this is the most accurate comparison possible.

B.3.11.2.2. Limitations

NAVIGATOR is a single-arm trial. Inevitably, using data from this trial comes with limitations in the validity of comparisons to other clinical data, as the treatment comparison is not strictly experimental. However, we have used patient-level data from BLU-285-1002 study and have followed NICE DSU TSD advice to do so. We therefore suggest that we have made the most robust comparison to clinical data that is possible at this time.

The BLU-285-1002 data do not have a baseline of initiation of first TKI for unresectable or metastatic *PDGFRA* D842 GIST. Instead, the baseline in this data set is the absolute first TKI for GIST, which may be used in the adjuvant setting. Due to this, the data were re-baselined to match up with the NAVIGATOR data. This limited the number of patients to [redacted] and meant that ECOG and race could not be included in the logistic model to estimate propensity scores. However, since the data used have a comparable baseline to NAVIGATOR, we consider the IPW-adjusted Kaplan–Meier data used to remain the most robust available comparison given the data currently available on these patients. Finally, as the selection of this data set for the survival comparison is crucial to the model results, we also include a scenario analysis naively comparing ECM survival data from Cassier to the original NAVIGATOR data (before applying weightings). This does not have a considerable effect on the estimated ICER.

There are currently no available HRQL data in patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST that can be used in the cost-effectiveness analysis required for a NICE submission. In the absence of other options, we have assumed that the *PDGFRA* D842V mutation does not have a discernible effect on patient HRQL, and this assumption was validated with clinical experts. However, as these values have been used in previous decision making in this disease area, it does allow for consistent decision making.

B.3.11.3. Avapritinib as a candidate for the cancer drugs fund

There is a clear unmet medical need in this indication, resulting from the high disease burden, low life expectancy and lack of any effective treatment. Avapritinib has demonstrated long-term OS and PFS for patients with unresectable and metastatic *PDGFRA* D842V-mutated GIST in the NAVIGATOR study. However, Blueprint Medicines acknowledges the remaining uncertainty surrounding the extent of the benefits with respect to overall survival and patient HRQL. Over the coming years, later data cuts from NAVIGATOR will become available, which will reduce uncertainty relating to the extrapolation of survival benefit. Furthermore, the VOYAGER study, which includes measurement of HRQL, will help to reduce uncertainty surrounding patient utility.

Therefore, Blueprint Medicines is seeking a recommendation for avapritinib for use within the CDF as a treatment for adults with unresectable or metastatic *PDGFRA* D842V GIST.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional clinical data from the NAVIGATOR study

Appendix M: Base case parameters and distributions

Appendix N: Inverse propensity score weighting

Appendix O: Additional model information

Appendix P: Cassier et al. clinical parameters and variables (efficacy scenario)

Appendix Q: Mix of TKIs as in BLU-285-1002 study (ECM arm scenario)

Appendix R: Resource use scenario

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment pathway in economic model	
Which treatments are used in 1st, 2nd and 3rd line established clinical management in the NHS in England?	**No standard treatments are available for PDGFRA D842V mutated GIST. Before advent of avapritinib some patients were treated with Imatinib to see if a symptomatic response could be achieved. There is retrospective data to support a modest response to the same. (Eur J Cancer 2017 May;76:76-83) No treatments standardly used beyond 1st line**
What proportion of patients receive 1st, 2nd and 3rd line established clinical management in the NHS in England?	**PDGFRA D842V is a rare GIST mutation- it is difficult to estimate. I would say >50% of patients with advanced D842V GIST will have received imatinib but very few receive 2nd line or beyone**
Issue 2: Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs	
Are the populations in the studies generalisable to the population that would be seen in the NHS in England, in terms of prior TKI treatment?	**Yes – broadly although more patients in other countries will have received more lines of therapy. Please see my separate response to NICE Clinical engagement questions**
Would the treatment effect be similar for people who have received prior therapy with TKIs to those who have not?	**Yes- if anything those who have not received prior TKI may well be of better performance status but this is a generalisation**
Issue 4: Modelling time on treatment	
Which extrapolation distribution curve best represents the most accurate clinically plausible results for time on treatment?	
Issue 5: Extrapolation of overall survival	

What proportion of patients receiving avapritinib would you expect to be alive at 2, 5 and 10 years?	
What proportion of patients receiving established clinical management would you expect to be alive at 2, 5 and 10 years?	Please see my replies to NICE clinical engagement question about overall survival of patients with advanced D842V GIST- this is around 15 months according to published data
Which extrapolation of overall survival is most clinically plausible?	N/A
Issue 6: Extrapolation of progression-free survival	
Which extrapolation of progression-free survival for 2nd and 3rd line established clinical management is most clinically plausible?	N/A
Issue 7: Treatment waning effect	
What is the most plausible assumption of treatment waning effect for avapritinib?	Currently there is no data in the public domain to support this statement
Issue 8: Utility values in the economic model	
Which utility value best represents progression-free survival in the 1st line setting?	N/A
Issue 9: End of life criteria	
Under established clinical management (that is, imatinib [1st line], sunitinib [2nd line] and regorafenib [3rd line]), is the life expectancy of people with unresectable or metastatic PDGFRA D842V-mutated GIST more than 24 months?	No- median OS is around 15 months for those with metastatic disease

Does avapritinib extend life for more than 3 months for people with unresectable or metastatic PDGFRA D842V-mutated GIST compared with established clinical management?	Yes- as per results of NAVIGATOR study (Lancet Oncol 2020 Jul;21(7):935-946.) Overall survival 91% at 12 months and 81% at 24 months
Issue 9: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	Additional data collection would be beneficial
Is avapritinib a good candidate for use in the Cancer Drugs Fund?	Yes but given the strength of the data seen should be approved outright

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

ERG critique of the company's response to the Technical Engagement Report

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Date completed

11th September 2020

Treatment pathway in the economic model

1.1 Which treatments are used in 1st, 2nd and 3rd line established clinical management in the NHS in England?

The company maintain their original assumption that all patients who receive ECM would receive imatinib 1st line, sunitinib 2nd line and regorafenib 3rd line. However, the ERG's two clinical expert advisors both agreed that few patients in the ECM arm would receive these TKIs due to their lack of efficacy, and those who do would mostly receive only imatinib (ERG report section 4.2.4). Two consultee submissions were received by NICE in response to Technical Engagement (Dr Benson, Professor O'Donoghue) which both concur with the ERG view.

1.2 What proportion of patients receive 1st, 2nd and 3rd line established clinical management in the NHS in England?

The company have not answered this specific question about which proportion of patients would receive these lines of therapy in clinical practice. Instead, they maintain the position in their original submission that all patients in the ECM arm would receive TKIs in the sequence of imatinib, sunitinib, and regorafenib, according to NICE guidance. However, the company do not explain why the NICE guidance, which is for the general GIST population, should apply to patients with the PDGFRA D842V mutation in whom the TKIs lack efficacy.

The company suggest that, if the ERG's assumption that few patients would receive TKIs is adopted, then survival in the ECM arm should be reduced since patients receiving best supportive care "will have worse outcomes than patients receiving TKIs". The company provide a speculative argument to support this assumption but no direct clinical evidence.

We note that the company's original submission states that the TKI treatments in the ECM arm have a lack of efficacy in this population with very low overall response rates and this was confirmed by the company's clinical experts (CS section B.3.3.3.1, p105). The company's arguments therefore appear inconsistent. As noted under Issue 1.1 above, clinical experts advising the ERG agreed that TKIs have lack of efficacy in patients with the PDGFRA D842V mutation, and few patients would receive TKIs in clinical practice.

2 Generalizability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs

2.1 Are the populations in the studies generalisable to the population that would be seen in the NHS in England, in terms of prior TKI treatment?

NAVIGATOR: The company state that the survival benefit of avapritinib is likely to be underestimated in the NAVIGATOR study relative to UK clinical practice because the outcomes of patients treated at first-line are likely to be better than those of patients at later lines, given the ineffective nature of other TKIs. The ERG and both our clinical expert advisors agree with this rationale.

BLU-285-1002: The company state that if it is assumed that most patients with PDGFRA D842V GIST are untreated in the UK then patients receiving ECM in study BLU-285-1002 would be likely to outperform those in UK clinical practice. However, the rationale for this is unclear, since prior TKIs received in BLU-285-1002 would not be expected to have efficacy in this mutation subgroup. Although it might be expected that line of TKI could be a proxy for duration of disease and hence performance status in BLU-285-1002, it is unclear how this can be compared to UK patients, most of whom would not be expected to receive TKIs despite potentially varying in their performance status. We therefore believe that the generalisability of the BLU-285-1002 study to UK practice is uncertain.

2.2 Would the treatment effect be similar for people who have received prior therapy with TKIs to those who have not?

As noted in Issue 2.1 above, the company state that survival in NAVIGATOR is likely to be an underestimate compared to UK clinical practice, where avapritinib will primarily be given as a first-line therapy.

We agree, and our clinical expert advisors concurred, that patients treated with avapritinib earlier in the disease process may have better outcomes than those treated after one or more TKIs. However, we also note that these patients may also spend more time on avapritinib treatment (even if there was better survival in patients who had not received prior therapy with TKIs it would not necessarily follow that there would be improvement in cost effectiveness).

3 Modelling time on treatment: Which extrapolation distribution curve best represents the most accurate clinically plausible results for time on treatment?

The company agree with the ERG's suggestion of using the Weibull distribution for modelling time on treatment.

4 Extrapolation of overall survival

4.1 What proportion of patients receiving avapritinib would you expect to be alive at 2, 5 and 10 years?

Further clinical consultation may be helpful to reduce uncertainty in this question

4.2 What proportion of patients receiving established clinical management would you expect to be alive at 2, 5 and 10 years?

Further clinical consultation may be helpful to reduce uncertainty in this question

4.3 Which extrapolation of overall survival is most clinically plausible?

We note that the company use a Weibull distribution to model OS for avapritinib in their updated analysis, as recommended by the ERG.

5 Extrapolation of progression-free survival: Which extrapolation of progression-free survival for 2nd and 3rd line established clinical management is most clinically plausible?

The company agree that the ERG's approach is reasonable. The ERG has no further comments on this issue.

6 Treatment waning effect: What is the most plausible assumption of treatment waning effect for avapritinib?

The company's updated base case assumes a post-discontinuation treatment effect duration of 18 months rather than 60 months, on the basis that this value is slightly below the midpoint between two suggestions provided in recent TKI NICE appraisals, TA621 (osimertinib) and TA463 (cabozantinib). Furthermore, the company state that, in both cases, clinical experts suggested that the benefit of TKI treatment extends beyond the period of active treatment, as the tumour(s) continue to shrink.

The ERG note that the appraisals suggested are for different indications. TA621 (osimertinib) is for non-small cell lung cancer and TA463 (cabozantinib) is for renal cell carcinoma. Therefore, there is uncertainty about whether assumptions used in these appraisals are generalisable to the current appraisal. We agree that the post-discontinuation treatment effect duration would be considerably shorter than 60 months.

As stated in the ERG report, the rationale for choosing only 1 month for the duration of post-discontinuation effect is that it provides a better fit against the study K-M data. As can be seen in the figure in the company's response (see Issue 4), choosing a longer post-discontinuation effect duration results in an overestimate of the OS for avapritinib compared to the study K-M data.

7 Utility values in the economic model: Which utility value best represents progression-free survival in the 1st line setting?

The company agree with the ERG's suggestion for analysing first line utility values but raise a concern regarding third line and progressive disease utility values.

In the ERG report, we recognised the relevance of the VOYAGER data and consequently included these as a scenario analysis. We agree that the VOYAGER data reflect the most recent evidence and are based on a large sample size of total GIST patients (i.e. all GIST patients including PDGFR D842V). Moreover, the experts advising the ERG considered that quality of life is similar among patients with GIST, regardless of their mutational status. However, we note that the third line utility value from VOYAGER (0.782) is higher than the

second line utility value used in the base case (0.781), which is considered to be unrealistic. But this is not expected to greatly impact the results. Therefore, we agree that the VOYAGER utility data are appropriate to be included in the ERG 's base case, however we were unable to incorporate this change in our base case in the time available. In addition, we note that the inclusion of VOYAGER utility data in the ERG's base case will slightly decrease the ICER from £125,309 to [redacted] per QALY (see Table 1 and Table 2 below).

8 End of life criteria

8.1 Under established clinical management (that is, imatinib [1st line], sunitinib [2nd line] and regorafenib [3rd line]), is the life expectancy of people with unresectable or metastatic PDGFRA D842V-mutated GIST more than 24 months?

The ERG consider that the life expectancy of these patients would be less than 24 months, as stated in the ERG report. The company's updated analyses based on the latest data cut for NAVIGATOR do not alter this conclusion.

8.2 Does avapritinib extend life for more than 3 months for people with unresectable or metastatic PDGFRA D842V-mutated GIST compared with established clinical management?

The ERG consider that avapratinib extends life for more than 3 months, as stated in the ERG report. The company's updated analyses based on the latest data cut for NAVIGATOR do not alter this conclusion.

9 Cancer Drugs Fund

9.1 Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?

The ERG agree with the company that approval of avapritinib for entry into the CDF would reduce some of the uncertainty in cost effectiveness by enabling the collection of more mature survival data.

The company also expect additional data to be available through the CDF on dosing and dose breaks. This may potentially enable investigation of whether patients treated with alternate day dosing would have the same efficacy as daily dosing. However, it is not clear how much new information may become available and there is a potential risk that uncertainty in the dosing regimen may not be reduced unless there are enough clinical cases with variations on the standard 300mg daily dose. It may be helpful to consider which types of dose regimen data would need to be sought, e.g. (i) alternate-day dosing with 300mg; (ii) use of reduced daily dosing <300mg; and/or (iii) information on avapritinib efficacy following discontinuation due to toxicity (but not discontinuation due to progression). Could data of types (ii) and (iii) allow direct inferences to be drawn about avapritinib efficacy under alternate-day dosing, given the mode of action of avapritinib? We note that some participants in NAVIGATOR received daily doses <300mg. These lower doses have not been separated in the CS but were instead pooled into the "all doses" group. Could these lower-dose data be extracted separately and, if so, would they be informative?

9.2 Is avapritinib a good candidate for use in the Cancer Drugs Fund?

The company's arguments appear reasonable. The ERG agree that avapritinib is a good candidate for the CDF since data on the clinical effectiveness and cost effectiveness of avapritinib in a UK setting are lacking (the pivotal NAVIGATOR study of avapritinib and the BLU-285-1002 study of ECM were not conducted in the UK and they included patients who had received higher burdens of prior TKI use than would be expected in NHS practice).

10 Additional Evidence

10.1 Update data cut from NAVIGATOR

The company have provided OS and PFS data from the latest data cut of NAVIGATOR. However, these have been incorporated directly into the company's updated economic model without comparison against the OS and PFS data from the original data cut.

In the interests of transparency, the ERG would have preferred to see a simple tabulation of the OS and PFS hazard ratios, with K-M curves, for both the original and latest data cuts, to show

how the latest data compare to those reported in the CS. We would also have preferred an option of comparing the original and latest data cuts in the company's updated model, to allow a demonstration of the impact of the updated survival data on model outputs.

As far as the ERG are aware, there are no reference documents available for the latest NAVIGATOR data cut (such as an updated interim CSR, company report, or conference abstract) against which the OS and PFS data in the updated company model can be validated. Without seeing a separate tabulation of the OS and PFS outcomes from the latest NAVIGATOR data cut we are unable to check whether there might be any errors in the latest OS or PFS data included the model.

10.2 Alternate-day dosing pattern

The company state that "Recent information provided by a UK-based clinical expert has indicated that some clinicians may use an alternate-day dosing pattern for avapritinib in clinical practice, where patients take a tablet of avapritinib at the same concentration every other day. This has also been supported by several other international clinical experts at an advisory board (reference 10)."

No specific information from the "UK-based clinical expert" has been provided by the company. Furthermore, reference 10 (GIST Advisory Board 10 February 2020), which is marked as data on file, has also not been provided by the company. The ERG therefore cannot validate the company's statement about alternate-day dosing.

The company provided further supporting information that efficacy of avapritinib could be maintained for some patients in clinical practice following discontinuation due to toxicity, citing an unpublished abstract written by a clinical expert at Leuven Cancer Institute in Germany (reference 11). This abstract reports cases of

[redacted]

[redacted]

Clinical experts advising the ERG agreed that these two case studies are interesting and could be considered hypothesis generating but should not be taken as evidence that all patients will experience a prolonged post-treatment effect.

10.3 Updated base-case analysis

For model verification, the ERG reproduced the company updated cost effectiveness results (presented in Table 2 of company's Technical Engagement response form) by incorporating all the necessary changes to the model assumptions, as listed in Table 1 of company's Technical Engagement response form. No errors were identified. We also reproduced most of the scenario analyses conducted by the company in Table 7 of company's Technical Engagement response form, except two scenarios as shown in Table 3.

In addition to the above, we updated our preferred base case model with the updated March 2020 data cut. The results are shown in Table 1 below. We notice a slight increase in ICER from [redacted] (original January 2020 data cut) to £125,309 (updated March 2020 datacut). We also conducted two additional scenario analyses (shown in Table 2 below) on our preferred base case model with updated March 2020 datacut. Changing the dosing pattern had a significant impact on the cost- effectiveness results as the ICER is reduced to [redacted] compared to [redacted] (ERG preferred base case with March 2020 datacut), although it remained above the NICE willingness-to-pay threshold of £50,000 per QALY.

Table 1: Cost effectiveness results of the ERG's preferred base case with the company's updated data cut

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company original base case (ERG corrected)	Avapritinib	[redacted]	[redacted]	
	ECM	[redacted]	[redacted]	£50,033
ERG preferred base case with original data cut January 2020	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
ERG preferred base case with updated data cut March 2020	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	£125,309

Table 2: Scenario analyses conducted on the ERG's preferred base case with the company's updated data cut

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Alternate-day dosing	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Utilities (VOYAGER + cap)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]

Table 3: Inconsistencies between ERG and company scenario analyses from Table 7 in the company's Technical Engagement response form

Scenario: ECM TKIs from BLU-285-1002	**Company ICER**	**ERG ICER**
Without alternate-day dosing	[redacted]	[redacted]
With alternate-day dosing	[redacted]	[redacted]
Scenario: OS avapritinib log-logistic	**Company ICER**	**ERG ICER**
Without alternate-day dosing	[redacted]	[redacted]
With alternate-day dosing	[redacted]	[redacted]

Response to NICE request for additional analysis

1 NICE requests

Following technical engagement, NICE has requested the following:

- analysis and resultant ICERs using modelled overall survival taken directly from extrapolation of the full OS data from the NAVIGATOR IPW analysis – uncensored for discontinuation – March 2020 data cut - with the post technical engagement preferences applied (with and without alternate-day dosing). If you could please supply analysis using the full range of extrapolations (exponential, Weibull, Gompertz, log-normal, log-logistic) and resultant ICERs.

- analysis and resultant ICER using modelled overall survival taken directly from extrapolation of full OS data from the NAVIGATOR IPW analysis – uncensored for discontinuation – March 2020 data cut for the patients in NAVIGATOR who did not receive previous treatment with a TKI (i.e. first line). If you could please supply analysis using the Weibull model.

2 Responses

2.1 Direct extrapolation of overall survival

Firstly, we interpret “post technical engagement preferences” to refer to the revised company base-case following the technical engagement meeting. We hope that this was the intended meaning.

Figure 1 shows the results of simple extrapolation of overall survival data from NAVIGATOR, using the updated data cut. Table 1 provides a summary of statistical information criteria, including the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Statistical fit indicates the exponential and Weibull models to be statistically similar, as the statistics are within 5 of each other. However, the extrapolation with exponential has a poor visual fit to the available Kaplan-Meier data, whilst the Weibull model provides a pessimistic extrapolation of overall survival along with Gompertz.

In a situation such as this, the advice contained within NICE DSU TSD 14 suggests that the clinical plausibility of the different extrapolations be taken into consideration when selecting the most appropriate model to characterise the survival of the population.[3] The best fitting models provide survival extrapolations which are potentially either side of the true value (See Table 2), whilst the log-logistic and log-normal extrapolations provide a middle ground whilst having very similar visual fit to the Kaplan-Meier data to the Weibull extrapolation. **We suggest, therefore, that the log-logistic or the log-normal extrapolation is used for decision making.**

[redacted]

Table 1 Statistical fit of survival models, NAVIGATOR updated data cut

Fit Statistics	AIC	BIC
Exponential	**115.18**	**117.21**
Weibull	**111.93**	**115.98**
Gompertz	144.21	148.26
Log-normal	138.52	142.57
Log-logistic	139.81	143.86

Table 2 presents ICERs with and without alternate-day dosing, using standard extrapolation of the observed Kaplan-Meier from the NAVIGATOR, i.e. without explicitly simulating the discontinuation of the treatment and its effects on the overall survival.

Table 2: ICERs with and without alternate-day dosing, using standard extrapolation

	Undiscounted total LYs for avapritinib	ICER without alternate-day dosing	ICER with alternate-day dosing
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost effectiveness ratio; LY, life-year.			

It is important to note that there are several reasons to interpret this analysis as extremely conservative:

- Clinical experts have repeatedly confirmed that prognoses for patients treated at 1L would be better than those at later lines, meaning a mixed-lines overall survival Kaplan–Meier is likely to be a considerable underestimate of overall survival in clinical practice
- There is evidence to suggest that a post-discontinuation treatment effect is associated with avapritinib, as previously shared with NICE, which should be reflected in the modelling. This evidence is described in detail in the company response to Issue 6 during technical engagement, and includes:
  - Statements in support of this notion from clinical experts based on their observations (including an abstract written by a clinical expert[1] and a recent advisory board conducted by Blueprint Medicines[2])
  - The fact that most discontinuations ([redacted]) in the NAVIGATOR trial were due to toxicity, where a post-discontinuation treatment effect is more likely to occur, as these patients were not discontinued due to loss of treatment effect
  - Precedent from previous appraisals
- The simple extrapolation of overall survival provides a very conservative estimation of expected overall survival (6.26 – 6.75 years, using the log-logistic or log-normal models). This is comparable with the mean overall survival of 6.66 years obtained in the ERG

preferred base case, with 1-month post-discontinuation treatment effect, which as discussed above is highly conservative.

2.2 Analysis in first-line patients from NAVIGATOR

In the NAVIGATOR study, [redacted] patients received avapritinib as a first line (1L) treatment. The NICE team requested the analysis and resultant ICER using modelled overall survival taken directly from extrapolation of full OS data for the patients in NAVIGATOR who did not receive previous treatment with a TKI (i.e. first line), only with the Weibull extrapolation.

However, given that this is a new and distinct analysis of survival data for avapritinib patients, we feel that it would be more appropriate to follow the usual NICE process, which includes selection of appropriate survival models using the advice contained within NICE Decision Support Unit Technical Support Document 14.[3]

In the 1L analysis, the Weibull model is no longer the statistically best-fitting. Table 3 presents the Akaike information criterion (AIC) and Bayesian information criterion (BIC) of the updated analysis in 1L NAVIGATOR patients, and Figure 2 shows the extrapolated survival results.

Table 3: Overall survival statistical fit – avapritinib at first line, March 2020 data-cut, no censoring for discontinuation, IPW adjusted

Fit Statistics	AIC	BIC
Exponential	**33.40**	**33.80**
Weibull	**33.76**	**34.55**
Gompertz	50.11	50.91
Log-normal	48.84	49.64
Log-logistic	49.05	49.85

[redacted]

[redacted]

The exponential model has the best fit, however, when observing Figure 1, it has a poor visual fit to the Kaplan–Meier data. Conversely, the Weibull presents a pessimistic extrapolation whilst also having a good visual fit to the Kaplan-Meier data. The Gompertz model has a poor visual fit, the worst statistical fit of all the models, and a very pessimistic extrapolation. The log-logistic and log-normal extrapolations have very similar visual fit to the Weibull to the available Kaplan-Meier data, but provide a middle-ground between the Weibull's pessimistic extrapolation and the optimistic extrapolation of the exponential, which are both statistically equivalent as the AIC and BIC are very close.

In this context, judging the most appropriate extrapolation based on only statistical fit and visual appraisal may not be sufficient. Clinical plausibility of the resultant expected overall survival must be central to the decision made. Considering the tight timeline on delivery of this analysis, we were not able to consult clinical experts about the plausibility of these estimates. However, during previous engagement with clinical experts, a mean overall survival of 10.40 years was considered plausible for patients receiving avapritinib at 1L.[4]

Based on this, all the simple extrapolations of 1L avapritinib OS from NAVIGATOR are pessimistic (with the Weibull being 4.46 years). However, the models that have the best visual fit to the Kaplan-Meier data whilst also balancing the expectations of clinical experts are the log-normal and log-logistic (in that order). We would therefore argue that it is these extrapolations and not the Weibull extrapolation which should be used for decision making in this scenario.

The resulting ICERs and estimated undiscounted life years (i.e. expected overall survival) in the avapritinib arm are presented in Table 4.

Table 4: ICERs with and without alternate-day dosing, using standard extrapolations of 1L overall survival data (original IPW analysis of BLU-285-1002)

	Undiscounted total LYs for avapritinib	**ICER without alternate-day dosing**	**ICER with alternate-day dosing**
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost effectiveness ratio; LY, life-year.			

In the NAVIGATOR study, [redacted] patients received avapritinib as a first line (1L) treatment, [redacted] of whom were UK patients. The median follow-up in the NAVIGATOR study was 25.5 months and the Kaplan-Meier is highly immature. The outcomes, both in terms of extrapolated overall survival and ICER from the model, are not significantly different from those obtained with the overall D842V cohort. Clinical experts have repeatedly confirmed that prognoses for patients treated at 1L would be better than those at later lines, however we believe that this is not apparent from the 1L subgroup in NAVIGATOR, because of the too small number of patients and of the too short duration of observation.

Therefore we believe that this subgroup of patients constitutes an insufficient evidence base for decision making, and is also unlikely to be representative of all UK patients with unresectable or metastatic *PDGFRA* D842V GIST treated with avapritinib at 1L. Blueprint Medicines is committed to addressing this issue to the best of its ability by participating in the

registry data collection as part of the conditional European Medicines Agency approval. This registry will specifically focus on patients treated with avapritinib in 1st line and will be supplementing the number of observations and duration of follow up that can be used to inform cost-effectiveness estimates.

In conclusion, the level of uncertainty surrounding this analysis is considerable and the results are likely to be biased simply due to the extremely small sample size. Therefore, we believe that the 1L analysis should only be used for reference and not for decision making.

References

1. Schöffski P. Responses to avapritinib in tumors with PDGFR α-D842V mutation persist after treatment discontinuation: an unprecedented finding in advanced gastrointestinal stromal tumors (GIST) and scientific rationale for alternative dosing schedules and potential adjuvant use of the agent. 2020. Data on File.
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3. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed: 05 March 2020.
4. Blueprint Medicines Corporation. Internal correspondence with clinical expert. 29 October 2019. Data on file.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

ERG critique of the company's additional analyses provided after Technical Engagement

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Date completed

2nd October 2020

Analyses conducted by the company

In response to a request from NICE following Technical Engagement (TE), the company provided the following additional analyses:

Additional analysis 1

An analysis and resultant ICERs using modelled overall survival taken directly from extrapolation of the full OS data from the NAVIGATOR inverse probability weighting (IPW) analysis, following these criteria:

- uncensored for discontinuation
- using the March 2020 data cut
- applying the post TE preferences (with and without alternate-day dosing)
- presented for the full range of extrapolations (exponential, Weibull, Gompertz, log-normal, log-logistic) and resultant ICERs

Additional analysis 2

As analysis 1 but restricted to the patients in NAVIGATOR who did not receive previous treatment with a tyrosine kinase inhibitor (i.e. first line patients) and using the Weibull extrapolation only.

ERG critique of the company's analyses

Model validation

The ERG have checked and verified the company's analyses in the updated company economic model. The updated analyses were appropriately implemented in the economic model and we were able to reproduce the cost-effectiveness results reported by the company in Table 2 and Table 4 of their response document. The full results for the log-normal and Weibull extrapolations are shown in Table 1 below.

Table 1: ICERs without alternate-day dosing, using standard extrapolation

	Undiscounted total life years for avapritinib	Discounted QALYs for avapritinib	Discounted costs without alternate-day dosing	ICER without alternate-day dosing
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Comments on company additional analysis 1

The company suggest that the log-normal or log-logistic extrapolations should be used. As noted in the ERG report, the NICE DSU Guidance Document 14 states that the same distribution would be appropriate for both treatment arms. We do not consider that the company have provided compelling evidence to support their argument that different distributions should be used in the two treatment arms. Further, we consider the Weibull is the best fit for the ECM arm (see ERG report section 4.2.6). Therefore, we consider a Weibull distribution should be used for both avapritinib and ECM.

Comments on company additional analysis 2

For the analysis in first-line patients from NAVIGATOR, the company note that the outcomes, both in terms of extrapolated overall survival and the ICER from the model, are not significantly different from those obtained with the overall PDGFRA D842V cohort. We agree with this statement.

We also agree that these results for first-line patients should be treated with caution, given the small sample size.

Comparison of survival estimates between the different modelling approaches

We present a comparison of the survival estimates for additional analysis 1 (with log-normal and Weibull distributions) and the company's updated base case (as used in their TE response) in Table 2 and Figures 1-3 below. We note that the OS is much higher at 5 years ([redacted]%) in the company's updated base case model with OS censored for discontinuation, linked to ToT and extrapolated using a Weibull distribution compared to the estimates using the additional analysis

with OS uncensored for discontinuation and a simple extrapolation using the log-normal ([redacted]%) or Weibull distribution ([redacted]%).

Table 2: Comparison of the OS estimates with and without censoring for discontinuation

	Updated base case model with OS censored for discontinuation, linked to ToT and extrapolated using Weibull		**Updated model for additional analysis 1, with OS uncensored for discontinuation; simple extrapolation using log-normal**		**Updated model for additional analysis 1 with OS uncensored for discontinuation; simple extrapolation using Weibull**	
Time	**Avapritinib**	**ECM**	**Avapritinib**	**ECM**	**Avapritinib**	**ECM**
1 year	[redacted]	45%	[redacted]	45%	[redacted]	45%
2 years	[redacted]	29%	[redacted]	29%	[redacted]	29%
3 years	[redacted]	20%	[redacted]	20%	[redacted]	20%
4 years	[redacted]	14%	[redacted]	14%	[redacted]	14%
5 years	[redacted]	11%	[redacted]	11%	[redacted]	11%
ECM: established clinical management; ToT: time on treatment						

Figure 1: Updated model Post TE with OS censored for discontinuation, linked to ToT and extrapolated using Log-normal

Figure 2: Updated model Post TE with OS uncensored for discontinuation, simple extrapolation using log-normal

Figure 3: Updated model Post TE with OS uncensored for discontinuation, simple extrapolation using Weibull

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Clarification questions

May 2020

File name	Version	Contains confidential information	Date
		Yes	

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Clinical study reports

A1. Priority question. Please provide the following missing clinical study reports/report sections:

(a) The clinical study report, including the statistical analysis plan, for the NAVIGATOR study January 2020 data cut (Document B reference 46).

The January 2020 data cut was compiled to address day 120 questions from the European Medicines Agency (EMA), as part of the regulatory process. It is therefore not associated with an updated clinical study report (CSR). The original NAVIGATOR interim CSR (November 2018 data cut) was provided to the Evidence Review Group (ERG) alongside the original submission, and the final CSR for NAVIGATOR will not be available until 2022. The statistical analysis plan (SAP) for NAVIGATOR will be provided alongside these responses.

(b) The interim clinical study report, including the statistical analysis plan, for the VOYAGER study.

As discussed in the clarification call on 19 May 2020, no CSR is currently available for the VOYAGER study, and this will not be available until the [redacted]. However, the SAP is available and will be provided alongside these responses.

(c) The statistical analysis plan for the NAVIGATOR interim clinical study report (Appendix 16.1.9 in Document B reference 47).

The original SAP for NAVIGATOR will be provided alongside these responses.

(d) The statistical analysis plan for the BLU-285-1002 study clinical study report (Appendix 16.1.9 in Document B reference 60).

The original SAP for BLU-285-1002 will be provided alongside these responses.

Indirect treatment comparison

A2. According to CS Appendix D (page 26), "some factors potentially associated with treatment outcomes were identified" from the scientific literature.

(a) Please provide the evidence that was used to determine which of the identified factors are prognostic and whether all relevant prognostic factors have been identified.

As unresectable or metastatic *PDGFRA* D842V-mutated gastrointestinal stromal tumour (GIST) is extremely rare (at approximately five incident cases in the UK each year) with poor prognosis given current treatments, no established evidence on prognostic factors exists. Consequently, we opted for an inclusive approach, including all potentially relevant parameters. Therefore, covariates were selected primarily based on availability and completeness in both datasets.

Following the sensitivity analyses conducted at the ERG's request (see questions A4, A6, A7, A9 and A11), we conclude that due to the low number of observations, no superior, reasonable alternative approach to accommodate differences in characteristics is available. Furthermore, the extensive sensitivity analyses presented here demonstrate that the propensity scoring approach has little bearing on the results. Finally, the treatment of data has been shown to also have little impact on the results.

(b) Are any known prognostic factors missing from the individual patient data?

As noted above, there are no known prognostic factors specific to this indication. We suspect that Eastern Cooperative Oncology Group (ECOG) status could be related to outcomes as this is often the case in oncological indications. However, the high proportion of missing data meant that we could not perform propensity scoring, and therefore could not reasonably match up the datasets when including this parameter. Other than this, we included all the parameters that were available to us. These factors are listed in Table 8 of the CS Appendix D (page 26).

A3. A comparison of baseline characteristics for NAVIGATOR and BLU-285-1002 is presented in CS document B Table 15. Is this list comprehensive or are there other patient-level data for potential prognostic factors available?

We confirm that this list is comprehensive, including all factors that were available in both datasets (i.e. at initiation of avapritinib in NAVIGATOR, and at initiation of first TKI for treatment of unresectable or metastatic GIST for BLU-285-1002 study).

A4. Priority question. Please explain why age and disease duration were dichotomised in the propensity score matching:

(a) What prompted the choice of cut off for age (<60, ≥60 years) and disease duration (<3 years/≥3 years), is there evidence of a prognostic effect at these levels?

Age and disease duration were categorized using approximately the average (mean age at start of reference treatment = [redacted] years; mean duration of the disease at start of reference treatment = [redacted] years) within the dataset, to make the variables describe patients that were above or below average. Although there was no clear prognostic effect explored at these specific 'cut-points', we chose to dichotomize the continuous variables for two reasons; i) to avoid making the assumption of linearity of effect required when including such variables as continuous, and ii) to avoid exploring more flexible categorization (> 2 categories) for each variable due to a lack of patient numbers to support such analyses.

As shown in response to Question A4b below, sensitivity analysis on these definitions or treating the variables as continuous makes very little difference to the results, both in terms of statistical fit of the propensity scoring logistic regression and the subsequent Kaplan–Meier data.

(b) Was a sensitivity analysis conducted using categorical variables? If so, what was the impact on the analysis? If a sensitivity analysis was not done originally, please conduct this.

To test the sensitivity of the results on the selected approach to categorize or describe the patient population, we have conducted several sensitivity analyses. These include:

- Treating age and disease duration as continuous variables
- Treating just age as continuous
- Treating just disease duration as continuous
- Changing the cut-off for age to 55 (keeping disease duration as it is)
- Changing the cut-off for disease duration to 2 years (keeping age category as it is)

Below we report the results of this sensitivity analysis. As the data being used in each case are the same (for this scenario analysis), models can be compared using an information criterion. Table 1 reports fit statistics from the logistic regression to estimate propensity scores (PS) in the original inverse probability weighting-adjusted (IPW-adjusted) analysis and the five tested scenarios. This table shows that there is no statistical improvement to the fit of the propensity model versus the one included in the original submission.

Table 1: Propensity model fit statistics

Propensity model	Null deviance (df)	Residual deviance (df)	AIC
Original submission	[redacted]	[redacted]	[redacted]
Age and disease duration as continuous	[redacted]	[redacted]	[redacted]
Just age as continuous	[redacted]	[redacted]	[redacted]
Just disease duration as continuous	[redacted]	[redacted]	[redacted]
Age dichotomy at 55 years	[redacted]	[redacted]	[redacted]
Disease duration dichotomy at 2 years	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion; df, degrees of freedom.			

Figure 1: Overall survival Kaplan–Meier plots of scenario analysis applied to data treatment for age and disease duration

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Figure 2: Progression-free survival Kaplan–Meier plots of scenario analysis applied to data treatment for age and disease duration

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Furthermore, Figure 1 and Figure 2 show the original IPW approach to be approximately central to the other IPW estimates, which do not considerably vary from analysis to analysis.

A5. Priority question. Please provide further information on the Stata analysis method:

(a) Which Stata module was used for the analysis (e.g. teffects)?

No modules outside of core Stata functionality were required. The propensity scoring model takes the form of a simple logistic regression, as there is only one observation per patient. The process of IPW is provided below, along with the code used:

- PS was estimated as a logistic regression with the command

  logit treatment_study gender age_dummy anatomical_site metastatic_disease total_tki_dummy duration_dummy

  where the dependent variable treatment_study was equal to 1 for patients from NAVIGATOR and equal to 0 for patients from BLU-285-1002

- The command *predict ps* was used to generate the PS for each patient

  Inverse probability weightings (IPW, IP weights) were calculated from the estimated PS, using the following commands:

  gen ipw_weight=1/ps if treatment_study==1
  replace ipw_weight=1/(1-ps) if treatment_study==0

(b) Please provide the Stata code used for the propensity score matching, including the individual patient data.

The requested .do files are provided alongside responses to these clarification questions.

A6. Priority question. Kaplan–Meier (KM) curves and median survival are reported but without hazard ratios and variance measures. Please provide the following missing hazard ratios and their confidence intervals:

(a) For the adjusted comparison between NAVIGATOR and BLU-285-1002 (CS Appendix N).

The hazard ratios and 95% confidence intervals for the IPW-adjusted comparisons of avapritinib vs ECM for both overall survival (OS) and progression-free survival (PFS) are provided below in Table 2.

Table 2: Hazard ratios confidence interval for original inverse probability-weighted Kaplan–Meier data from NAVIGATOR and BLU-285-1002

	Hazard ratio (95% confidence interval)
ECM vs avapritinib OS	[redacted]
ECM vs avapritinib PFS	[redacted]
Key: ECM, established clinical management; OS, overall survival; PFS, progression-free survival.	

(b) For the unadjusted comparison between NAVIGATOR and the Cassier study (CS Appendix P).

The hazard ratios and 95% confidence intervals for the unadjusted comparisons of avapritinib vs ECM (as from Cassier et al.) for both OS and PFS are provided below in Table 3.

Table 3: Hazard ratios and variance measures from unadjusted naïve comparison of NAVIGATOR and Cassier et al. 2012

	Hazard Ratio (95% confidence interval)
Cassier et al. vs avapritinib OS	[redacted]
Cassier et al. vs avapritinib PFS	[redacted]
Key: ECM, established clinical management; IP, inverse probability; OS, overall survival; PFS, progression-free survival.	

A7. Priority question. It is our understanding that the IPW method corrects for missing data, so please explain why predictors with missing values were excluded (CS Appendix N):

In general, the propensity score (PS) method per Section 2.3.2 of the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 17 is used to adjust for imbalances in the characteristics of two groups of patients. In our specific case, a multivariate logistic regression model was used to generate the PS. The individual values of PS for each patient were then used to generate individual weights.

Although weightings can be calculated after the fact by replacing missing values with zero values, it remains that the underlying logistic regression model is estimated after dropping those patients with missing values. Without imputation of missing data, this can lead to potential bias in the estimated coefficients.

Race was not included in part due to missing values ([redacted] in NAVIGATOR), and additional reasons for exclusion are provided in response B1a. For ECOG status, [redacted] observations are missing from the BLU-285-1002 data. Estimating propensity scores based on only [redacted] from BLU-285-1002 data is not appropriate.

(a) Why was race excluded from the analysis given that there are only a small number of missing data?

In addition to the missingness issue, the decision to exclude race was based on a lack of variation in the BLU-285-1002 dataset. As can be inferred from Table 58 in Appendix N.2, [redacted]. To include this parameter leverages much of the matching on very little variation in the parameter, which may bias the analysis. Despite this, we provide a scenario analysis including race, in answer to Question A7b. Note that information criteria cannot be compared to model fit for the other scenario analyses, as the two analyses use different numbers of observations (due to missingness in race).

(b) Was a sensitivity analysis conducted including race? If so, what was the impact on the analysis? If a sensitivity analysis was not done originally, please conduct this and provide the results.

Sensitivity analysis on inclusion of race to model specification

Including race does not make a considerable difference to OS or PFS in either arm (Figure 3 and Figure 4). However, it does increase OS in the ECM arm in the first 1,000 days, though the curves realign in the longer term.

Figure 3: Overall survival Kaplan–Meier including race in IPW analysis

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Figure 4: Progression-free survival Kaplan–Meier including race in IPW analysis

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

(c) Is there any evidence that the excluded predictors race and ECOG performance status are potential prognostic factors?

As discussed in the response to Question A2, no established evidence on prognostic factors exists in unresectable or metastatic *PDGFRA* D842V-mutated GIST, due to the extreme rarity and to the poor prognosis associated with the condition.

As shown in parts a and b, race makes very little difference to the results. A similar exploratory analysis including ECOG performance status was not possible, due to there being only [redacted] (of ECOG performance status 0) present in the BLU-285-1002 dataset.

A8. Priority question. Please explain how the regression coefficients presented in CS Document B Table 16 should be interpreted. Are these the propensity score weights?

The parameters in Table 16 of Document B are the parameters for the logistic regression per standard PS analysis. This has the following specification (see answer to A5):

$$ARM = \alpha + \beta_1 x_1 + \cdots + \beta_k x_k + \epsilon$$

Where the parameters 1 to k are the factors included in the analysis.

The fitted values from such a regression model are propensity scorings, describing the propensity of a patient to be in one of the arms (depending on which is defined as the reference category). The inverse probability weightings were then subsequently calculated using the standard method, which in our case is:

$$IPW_i = \begin{cases} if\ \ ARM_i = AVA, & then\ \ \dfrac{1}{(1 - PS_i)} \\ \\ if\ \ ARM_i = ECM, & then\ \dfrac{1}{PS_i} \end{cases}$$

An important consideration here is that the reference category in the regression analysis is NAVIGATOR (i.e. $ARM_i = AVA$). This means that the fitted values from the logistic regression are estimated probabilities of being part of the BLU-285-1002 cohort. Consequently, a higher fitted propensity score for an ECM patient is a *lower* estimated propensity to be in the NAVIGATOR dataset (as it suggests a high probability of BLU-285-1002 and low probability of NAVIGATOR). Thus, the weightings presented above are higher for lower fitted values on BLU-285-1002 data, and higher for higher fitted values on NAVIGATOR data.

These IPWs can then be used directly within statistical software commands to generate weighted Kaplan–Meier data and extrapolations based on those weighted data. In Stata, this is done when performing stset. For example, for OS with a 1-month time unit:

stset time_tx [pw=ipw_weight], failure(censor_os==0) scale(30.44)

In R, this is done when performing survival analysis itself. For example, when using survfit() or flexsurvreg(), there is simply an argument for “weights” where the weighting parameter can be entered. To test this, survival analysis was repeated in R (propensity scoring, IPW and survival analysis/extrapolation). This generated identical results throughout.

A9. Priority question. Two patients had high propensity score weights (CS Appendix N3), and thereby a potentially disproportionate impact on the analysis. What is the effect of removing these patients from the propensity score matching?

We do not agree with the ERG that removing patients from the dataset is a useful scenario. In our view, it would not be good practice to selectively remove BLU-285-1002 patients with high inverse probability weights (i.e. those that most closely represent the NAVIGATOR population) from the analysis because this would reduce the already small amount of data. Also, it would introduce arbitrary imbalance into the results, reducing the ability of the matching exercise to balance the datasets appropriately. Nevertheless, we present below the results of an analysis removing these two patients.

For context, plots of the weights applied to each individual patient in the two cohorts (using the original model specification) are presented below in Figure 5 and Figure 6. It is common for the larger dataset to have a more even spread of propensity scores.

Figure 5: Inverse probability weights for NAVIGATOR patients

Figure 6: Inverse probability weights for BLU-285-1002 patients

Removing the two patients with high scores

All patients with IPW above 10 were removed from the dataset and the propensity scoring repeated. The updated weights for BLU-285-1002 are presented in Figure 7. Note that two different patients now have weights over 10. The hazard ratio per Cox model is also provided (Table 5).

Removing the two patients from the original dataset increases the OS in the both arms (as both excluded patients died with relatively short survival times; see Table

4). However, as stated above, we do not believe this to be a valid analysis given that we have excluded data from the two patients that are most relevant to the overall included population. Excluding these two patients would reduce the validity of the IP analysis as the data are already very limited.

Table 4: Characteristics of the two patients dropped from the analysis for this scenario

Parameter	BLU-285-1002-01-003	BLU-285-1002-03-003
Sex	[redacted]	[redacted]
Age	[redacted]	[redacted]
Race	[redacted]	[redacted]
Tumour site	[redacted]	[redacted]
Metastatic disease	[redacted]	[redacted]
Disease duration at baseline (Years)	[redacted]	[redacted]
Previous TKIs	[redacted]	[redacted]
Overall survival time (days)	[redacted]	[redacted]
Progression-free survival time (days)	[redacted]	[redacted]
Key: TKI, tyrosine kinase inhibitor.		

Figure 7: Inverse probability weights when removing the two patients with high weights from the previous dataset (BLU-285-1002)

Table 5: Hazard ratios per cox proportional hazard model, when removing two ECM patients from matching dataset

	Hazard Ratio (95% confidence interval)
AVA vs ECM OS	[redacted]
AVA vs ECM PFS	[redacted]
Key: AVA, avapritinib; ECM, established clinical management; OS, overall survival; PFS, progression-free survival.	

A10. Priority question. Many of the post-matching absolute differences were higher than pre-matching (CS Appendix Table 58), suggesting that the matching between NAVIGATOR and BLU-285-1002 was not wholly successful. Was an a priori threshold set for matching?

To clarify on the approach used – the method was not propensity score matching, so there is no propensity score threshold. IPW based on propensity scoring analysis was used in place of propensity score matching because this allows for the inclusion of all data instead of removing a subset based on an arbitrary matching threshold. This was necessary due to the small number of observations in both studies. Removal of data in the context of limited observations is not ideal and can bias the analysis.

Table 58 in the Appendix reports the distribution of the characteristics in the two cohorts before and after PS weighting. As noted by the ERG, some characteristics have absolute differences that are slightly higher after inverse probability weights are applied. However, it should also be noted that the difference in the unadjusted distribution between NAVIGATOR and BLU-285-1002 was notable in only two parameters: age and number of total TKIs. In both cases (except for number of TKIs = 1), the weighting process reduces the absolute difference in means, leading to a cohort that has an overall better alignment. Other parameters were similar both before and after applying IPW. Further still, when removing many of these parameters (see answers to A11) from the analysis, the resulting IPW Kaplan–Meier data are not considerably affected.

We can therefore conclude that the adjustment with the PS weighting method between NAVIGATOR and BLU-285-1002 was mostly successful, and that changing of the model specification has little effect on the results.

A11. Priority question. DSU Technical Support Document 17 recommends that sensitivity analysis should be conducted with different matching methods (e.g. regression adjustment; IPW + regression adjustment) to test the stability of the results. Please provide the following information:

To clarify, propensity score 'matching' was not conducted. We tried to address imbalances in patient baseline characteristics using IPW, which uses propensity scores as weightings to individual patients in either dataset. This is distinct from matching in that there is no associated loss of data, which is desirable in this case given that there were only 19 observations for the BLU-285-1002 data.

> (a) The results of any sensitivity analyses conducted, with a clear description of the methods employed. If sensitivity analysis was not done, please conduct this, and provide a clear description of the approach used and the results.

As no matching was conducted, different matching methods are not relevant. However, various sensitivity analyses are reported throughout this document, in answer to questions A4, A7, A9, and A11b.

> (b) Did sensitivity analysis consider different sets of covariates and functional form (e.g. polynomials, interactions) of prognostic factors? What was the impact on the results?

In the submitted analysis, all available parameters for which there were sufficient data were included to provide as much information as possible to inform propensity scoring logistic model. This was also to include the parameters on which the subsequent alignment of the datasets would be appraised (i.e. the absolute difference in means in all the parameters included in the model, among some others).

However, we agree that more parsimonious models could be considered as scenario analyses. These can potentially improve predictive power, which, given the same set of observations, can be evaluated using AIC (for logistic regression).

As an additional scenario analysis, we repeated the exercise using a probit model to estimate propensity scores instead of a logistic model. Table 6 presents the result of a Cox proportional hazards model for the base case IPW approach, the parsimonious IPW approach, and the approach where the propensity scores were estimated using a probit rather than logistic model. The results across all approaches are very consistent.

Table 6: Comparison of hazard ratios using alternative IPW approaches

	AVA vs ECM	
	OS – HR (95% CI)	**PFS – HR (95% CI)**
Base-case IPW approach	[redacted]	[redacted]
Parsimonious IPW approach	[redacted]	[redacted]
Probit approach to IPW	[redacted]	[redacted]

Key: AVA, avapritinib; CI, confidence interval; ECM, established clinical management; HR, hazard ratio; IPW, inverse probability weighting; OS, overall survival; PFS, progression-free survival.

Stepwise model selection and resulting IPW analysis results

A backwards stepwise model selection process based on AIC associated with every possible combination of covariates was conducted. This used the *step()* command within the R package *stats* (part of the core R4.0.0 set). The results of this process are presented in Table 7. Removing all parameters except for the age dummy and the total TKIs dummy improves the statistical fit of the logistic regression model, which also coincides with those being the most imbalanced characteristics. However, this is at the expense of losing most information on potentially prognostic factors like gender, metastatic disease, and disease duration. Due to the limited data, we feel that it is unclear which of these is the better approach.

Table 7: Logistic regression for propensity scores, backwards stepwise model selection

Action to be taken / step of the process	DF	Resid. Dev	AIC
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion; DF, degrees of freedom; tki, tyrosine kinase inhibitor.			

Following this process, Kaplan–Meier plots were produced using the parsimonious propensity scoring model including only the dichotomous variables for age and the number of previous treatments (in their original categorical definitions).

Figure 8 and Figure 9 below present the base case IPW-adjusted Kaplan–Meier data and the Kaplan–Meier data adjusted by IPW using the more reduced model for

avapritinib OS, ECM OS, avapritinib PFS and ECM PFS. These plots show little difference between the two approaches to propensity scoring.

Figure 8: Overall survival Kaplan–Meier comparison, propensity scoring using reduced or full model specification

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability.

Figure 9: Progression-free survival Kaplan–Meier comparison, propensity scoring using reduced or full model specification

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability.

Probit regression model

In this scenario analysis a probit model was used to estimate propensity scores instead of a logistic model.

Figure 10 and Figure 11 below present the base case IPW-adjusted Kaplan–Meier data and the Kaplan–Meier data adjusted by IPW using the probit model for avapritinib OS, ECM OS, avapritinib PFS and ECM PFS. These plots show little difference between the two approaches to propensity scoring.

Figure 10: IPW overall survival – comparison between unweighted, logistic-based and probit-based propensity scoring method

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Figure 11: IPW progression-free survival – comparison between unweighted, logistic-based and probit-based propensity scoring method

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Section B: Clarification on cost-effectiveness data

B1. Priority question. Please explain why the NAVIGATOR study OS analysis censored discontinuation events (CS Document B Figure 13) rather than using the full OS data from the NAVIGATOR IPW analysis (CS Document B Figure 6). To enable us to assess the validity of the approach:

(a) Please clarify the number of patients who were censored for discontinuation.

[redacted] patients are censored for discontinuation.

The approach that the ERG suggests in Question B1c is the simplest approach to extrapolating the outcomes of the clinical trial. However, it should be considered that:

- Within the given data-cut in NAVIGATOR, [redacted] death events occurred over a maximum follow-up period of [redacted] months. Of these events, only one occurred while on treatment. [redacted] death events occurred after discontinuation of the treatment.
- Using the full OS data from the NAVIGATOR IPW analysis breaks any connection between ToT and treatment effect. This would preclude the modelling flexibility required to reflect the post-discontinuation gradual loss of treatment effect suggested to us by clinical experts. It is unlikely that this post-discontinuation treatment effect would be fully captured by the simple extrapolation of the full OS, due to the short follow-up period (and the consequent incomplete ToT data). Therefore, a more sophisticated approach linking ToT to OS was considered more appropriate, allowing a gradual loss of treatment effect to be explicitly (rather than implicitly) modelled
- Utilizing the full OS data from the NAVIGATOR IPW analysis does not account for the fact that better survival outcomes would be expected when using avapritinib at first line (as would be expected for the majority of patients in clinical practice) rather than in multiple lines (as is the case in NAVIGATOR). NAVIGATOR included patients at later treatment lines who may be less likely to benefit from treatment and therefore any post-discontinuation treatment effects.

The explicit modelling of discontinuation and residual treatment effect allows for the flexibility to consider a correction

For the above reasons, we implemented a more sophisticated solution, which separates out the probabilities of death, progression, and discontinuation. To do this, mortality for on-treatment patients was obtained from OS data in NAVIGATOR by censoring for discontinuation, and mortality for off-treatment patients was modelled using OS data for ECM. Furthermore, the death-censored PFS at later lines in the ECM data was used to isolate the rate of progression and apply it to post-avapritinib patients. Upon discontinuing treatment per the rate determined by the ToT extrapolation, patients lose the treatment effect and eventually align with the mortality rate of the ECM extrapolation (i.e. IPW BLU-285-1002).

(b) Please fit parametric curves to the IPW adjusted avapritinib Kapan–Meier data, without censoring for discontinuation, i.e. data as shown in CS Document B Table 17 and Figure 6.

Although we do not agree that this is the best approach to representing the value of avapritinib in these patients within UK practice (See answers to B1a and B1c), this analysis has been conducted.

Figure 12 and Figure 13 show the requested extrapolations of OS and PFS, respectively. Parameters are reported in Table 8 and Table 10. AIC and BIC are provided in Table 9 and Table 11, respectively. Selecting based on statistical fit and visual fit of the extrapolated line to the clinical data results in log-normal for both OS and PFS. The model requested by the ERG in B1c therefore includes a scenario applying this curve selection.

Figure 12: IPW-adjusted overall survival models – avapritinib (NAVIGATOR) and ECM (BLU-285-1002)

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Table 8: Parameters from extrapolations presented in Figure 12

Parameter	Estimate	SE	Estimate	SE
Exponential: lambda	[redacted]	[redacted]	[redacted]	[redacted]
Weibull: shape	[redacted]	[redacted]	[redacted]	[redacted]
Weibull: scale	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic: shape	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic: scale	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal: meanlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal: sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz: shape	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz: rate	[redacted]	[redacted]	[redacted]	[redacted]

Key: NA, not applicable; SE, standard error.

Table 9: Information criteria for extrapolations of overall survival (Figure 12)

	Avapritinib		ECM	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ECM, established clinical management.
Notes: Gompertz model did not converge using R version 4.0.0, command flexsurvreg()

Figure 13: IPW-adjusted progression-free survival models – avapritinib (NAVIGATOR) and ECM (BLU-285-1002)

Key: AVA, avapritinib; ECM, established clinical management; IPW, inverse probability weighting.

Table 10: Progression-free survival parameters from extrapolations presented in Figure 13

	Avapritinib		ECM	
Parameter	**Estimate**	**SE**	**Estimate**	**SE**
Exponential: lambda	[redacted]	[redacted]	[redacted]	[redacted]
Weibull: shape	[redacted]	[redacted]	[redacted]	[redacted]
Weibull: scale	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic: shape	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic: scale	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal: meanlog	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal: sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz: shape	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz: rate	[redacted]	[redacted]	[redacted]	[redacted]
Key: ECM, established clinical management; SE, standard error.				

Table 11: Fit statistics for extrapolations of progression-free survival per ERG request in Figure 13

	Avapritinib		ECM	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ECM, established clinical management; ERG, evidence review group.				

(c) Please submit an updated model and conduct a sensitivity analysis using the fitted survival models.

This sensitivity analysis has been included. Results of the original model and this scenario are presented in Table 12 and Table 13, respectively. Please note that the tunnel state for treatment waning cannot be applied in this scenario as it relies on modelling a link between ToT and OS, which requires censoring of avapritinib OS for discontinuation of treatment. Therefore, the tunnel state for treatment waning does not function in this scenario. This scenario also:

- Contradicts advice we have received from clinical experts that patients receive benefit from avapritinib beyond their period of treatment and that overall survival simulated in the base case represents a plausible estimation for patients treated with avapritinib
- Contradicts advice we have received from clinical experts that avapritinib would be given to patients in practice as a first-line treatment
- Is not able to factor in the impact that patients being treated at first line in clinical practice (instead of the mixed lines per the data) may have on the results

Therefore, considering all the clinical evidence and expert opinion that has been provided, we do not believe this scenario to be the most appropriate modelling approach.

Table 12: Original incremental cost-effectiveness results

	Total		Incremental		
	Costs	**QALYs**	**Costs**	**QALYs**	**ICER**
Avapritinib	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£49,996
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Table 13: Incremental cost effectiveness: scenario using uncensored overall survival

	Total		Incremental		
	Costs	**QALYs**	**Costs**	**QALYs**	**ICER**
Avapritinib	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£64,684
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

B2. Priority question. Please provide a validation of the economic model by comparing the model OS and PFS results against the observed data from the NAVIGATOR IPW analysis and the BLU-285-1002 study.

The requested comparison is shown in Figure 14. This shows that the modelled OS deviates from the OS Kaplan–Meier data from NAVIGATOR. This is expected, as the OS from NAVIGATOR is expected to underestimate survival outcomes that would be observed in clinical practice for the reasons laid out in the response to Question B1. In the base case submitted analysis it was assumed that the effect of treatment with avapritinib on mortality risk gradually waned over the course of 60 months after discontinuation. The resulting overall survival (mean [redacted] years) for patients treated with avapritinib was considered a plausible estimate by clinical experts. However, we acknowledge that there remains substantial uncertainty regarding the length of time over which the post-discontinuation treatment effect of avapritinib wanes, and we have thus provided OS extrapolations with various treatment effect waning durations for ease of comparison.

Figure 14: Comparison between modelled outcomes and clinical data, applying various durations of treatment waning

Key: AVA, avapritinib; ECM, established clinical management.

B3. Please explain why the unadjusted KM curve for PFS from the NAVIGATOR study shown in CS Document Figures 4 differs from the equivalent curve provided in the model Sheet!PFS_Data.

CS Document B Figure 4 presents the PFS of the NAVIGATOR *PDGFRA* D842V-mutated population before censoring for death events, which was necessary in order to establish the modelling framework used.

In the model, as explained and justified in Document B Section B.3.3, the PFS data used censors for death events. Within the framework of Markov models, it would be incorrect to independently model OS and PFS. To do so would be to assume that if probability of death is reduced, the OS curve would be lifted upwards and there would be no implications for PFS, which is unrealistic. This is because the probability of progression before death or death before progression (i.e. PFS) is assumed not to change when the probability of death at any time (i.e. OS) changes. Thus, an OS improvement with fixed PFS assumes that all extension of life is only for patients that have already progressed. Furthermore, as information on subsequent progression of disease after first line avapritinib are unavailable, assumptions on the rate of progression in subsequent treatment lines are necessary. We conservatively assume that the progression-rate benefit of avapritinib does not extend beyond first progression of disease.

The PFS used in the cost-effectiveness model is presented in CS Document B Figure 20. For convenience, Figure 15 below shows CS Document B Figures 4 and 20 superimposed so that the difference between them is clear. Note that the PFS censoring for death events is higher than the PFS not censoring for death (i.e. counting death as an event). This difference represents those patients who died whilst progression-free. To compensate for this, as can be seen in column L of the "Markov Avapritinib" sheet (and as described above), the respective probabilities of death and progression are summed together again to bring PFS back down, thus allowing changes in mortality to be reasonably reflected in PFS (which contains both death and progression events).

Figure 15: Comparison of progression-free survival with and without censoring for death events (NAVIGATOR)

B4. Priority question. Running the model PSA simulation gives errors in the mean PSA values for costs and QALYs in the avapritinib arm and these influence the cost effectiveness acceptability curve. Please clarify the reason for these errors and correct them if possible.

As discussed on the clarification call on 19 May 2020, we are unable to replicate these errors and the cause remains unclear. The probabilistic sensitivity analysis (PSA) code has been rewritten in the attached model, and this was tested five times with 1,000 iterations, with no errors. Please use the macro PSA2 instead of PSA. The original code is included for comparison. In case the issue still remains, even using the new macro PSA2, we are available to set up a video conference with the ERG technical team, to identify and troubleshoot any possible bug when the macro is running on ERG's machines.

B5. Please provide NHS reference cost codes for the adverse events of fatigue and dermatitis/rash (CS Document B Table 58).

Application of adverse event costs in prior appraisals for GIST (TA488, TA179 and TA86)[1-3] were limited. The adverse event costs used in prior submissions from wider

disease areas were therefore considered. For instance, TA581 is a recently published NICE submission that gave details on the assumed costs for several adverse events also considered in the avapritinib cost-effectiveness model.

Dermatitis/rash used the cost of a non-elective short stay (NHS reference cost code: Total HRGs – see Table 14): £589.07 per event, in line with the cost of a non-elective short stay used for rash in TA581 (Table 37 of the company submission dossier of TA581[4]). The cost of fatigue was similarly aligned to TA581 using the cost of a non-elective short stay (£589.07) plus the cost of a nurse visit (£6.45 – see Table 14), totalling £595.53 per event.

Table 14: Cost sources of fatigue and dermatitis/rash

	Total cost to the NHS 2018/2019	Total activity 2018/2019	Average cost per activity	Source
Non-elective short stay	3,704,159,230	6,288,114	£589	NHS reference costs 2018/19 (Total HRGs) – please see cell E14 of the 'Index' worksheet or cell M3 of the 'Total HRGs' worksheet
District nurse visit	N/A	N/A	£6.45	PSSRU 2019 (Table 10.2) - Nurse (GP practice) cost per hour including qualifications - assumed per patient contact lasting 9.22 minutes (i.e. equivalent to GP surgery average consultation in Table 10.3a) - £42 * (9.22minutes /60minutes) = £6.45
Key: GP, general practitioner; HRG, healthcare resource group; N/A, not available; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.				

B6. We are aware that data from the VOYAGER trial comparing avapritinib versus regorafenib are available (https://www.targetedonc.com/view/avapritinib-falls-short-in-third-and-fourth-line-gastrointestinal-stromal-tumors). Were HRQL data collected in VOYAGER? If so, please provide information on the HRQL data collection method and results for the *PDGFRA* D842V subgroup.

Only top-line data (as have been presented in the linked press release) are available from the VOYAGER study at this time. Health-related quality of life (HRQL) data

were collected in the VOYAGER study as European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) scores (secondary end-point) and as 5-level EQ-5D® (EQ-5D-5L) scores (exploratory end-point). The final CSR for VOYAGER is planned for the [redacted], and no interim CSR is planned. Based on the request from the ERG, analysis of HRQL data have been prioritized and currently ongoing. The results of the HRQL analysis from VOYAGER will be delivered to NICE in the shortest time frame possible.

The VOYAGER study was conducted in patients with locally advanced, unresectable or metastatic GIST undergoing treatment at third- or fourth-line. Only [redacted] out of the 476 patients included in this study ([redacted] patients in avapritinib arm and [redacted] in regorafenib arm) had the *PDGFRA* D842V mutation. The data presented from the VOYAGER study in the linked press release are for the overall patient population and therefore should not be considered relevant in relation to this submission. Data specific to the *PDGFRA* D842V mutation population from this study are not yet available. Furthermore, due to the low number of relevant observations, any quantitative estimates of HRQL of patients with *PDGFRA* D842V-mutated GIST will likely be unreliable for this decision problem. HRQL data from the overall VOYAGER population values may be useful once these data become available. However, any health state utility values derived from the VOYAGER intention-to-treat population would only be useful for third-line and progressive disease health states of the cost-effectiveness model, as VOYAGER includes only patients receiving third-line treatment or later, and line of treatment has a significant effect on HRQL due to the progressive nature of the disease.

In conclusion, while we acknowledge that uncertainty remains with regards to HRQL of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST, we believe that the health state utility values presented in the model (based on equivalent health state utility values accepted by NICE in previous appraisals for general unresectable or metastatic GIST) represent the most reliable data available. Data from the VOYAGER intention-to-treat population may be useful for informing HRQL in later treatment lines.

B7. Please confirm that time on treatment for ECM in the model uses PFS as a proxy.

We can confirm that in the framework of the modelled sequence of treatments, it was assumed that patients in the ECM arm are treated until progression.

B8. In the model the number of adverse events in the avapritinib arm appears to include patients in the SOC1/SOC2 health states. Please clarify how the incidence of adverse events has been calculated.

The incidence of adverse events has been calculated as a rate using the number of patients in the NAVIGATOR safety population ([redacted]) and the median follow-up time of [redacted] months (See sheet 'AE Data')

The calculation of adverse event incidence in the Markov sheets for both arms scale the number of events using the proportion of patients alive and on treatment in the avapritinib arm (See columns AE to BE in 'Markov Avapritinib'). The equation for avapritinib is:

$$N\_events, t \; = \; \%alive \; \times \% \; on \; treatment \mid alive \; \times monthly \; AE \; rate \; for \; that \; AE$$

As patients are not receiving subsequent therapies, no adverse events are associated with the SoC1, SoC2 and PD health states in the avapritinib arm.

For the ECM arm, the calculation is linked to the PFS of first-line, second-line and third-line treatment, then linking those rates to the correct reference table for adverse event rate depending on treatment. Please see cells AC to BC in the "Markov Comp" sheet of the model, which links proportion of patients on each treatment to its rate of adverse events, respectively.

$$N_{events,t} = \%alive \cap onIMA \times AErate_{IMA} + \%alive \cap onSUN \times AErate_{SUN} + \%alive \cap onREG \times AErate_{SUN}$$

B9. Priority question. In the model the time on treatment cost for avapritinib appears to include patients in the SOC1/SOC2 health states. Please clarify how time on treatment is calculated in the model for avapritinib.

The ToT data used censors for death and progression in order to isolate only the probability of patients discontinuing from avapritinib treatment. This allows it to be used independently of the probabilities of death and progression of disease. The per-cycle probability of discontinuation (before progression or death) is added to the probabilities of progression (before death) and death (at any time) to form the final ToT estimate, taking the respective probabilities of all three potential events into account. The resulting value in the Markov sheet is the percentage of patients remaining alive who are on treatment (these are the values contained in column "Markov Avapritinib"!Z:Z in the model). Therefore, in order to calculate the treatment cost, this must be scaled by OS, which is why the calculations in column CN includes the sum of all non-dead states. The equation in column CN of the "Markov Avapritinib" sheet is provided below for clarity:

$$E(c(AVA)_t) = \%\ alive \times \%\ on\ trt \mid alive \times 1\ month\ cost\ of\ AVA$$

B10. The utility decrements associated with each adverse event of grade 3-4 included in the analysis and the corresponding data sources are presented in CS Table 49. However, we have been unable to find the event utility decrements for anaemia and hypertension in the cited sources. Please clarify where these data were obtained from.

Application of adverse event utility decrements in prior GIST submissions (TA488, TA179 and TA86) were limited. The adverse event utility decrements used in prior submissions of wider disease areas were therefore considered. For instance, TA439 (MTA review of TA176 and partial review of TA240) gave details on disutility values for several adverse events also considered in the avapritinib cost-effectiveness model.

Table 15 provides a more comprehensive description of the source of the utility decrements used for anaemia and hypertension.

Table 15: Source of utility decrements for anaemia and hypertension

Adverse event	Disutility	Source
Anaemia	-0.08500	PenTAG (2015) - Table 126 (page 340) of the review of TA176 and partial review of TA240[5]
Hypertension	-0.069	PenTAG (2015) - Table 75 (page 212) of the review of TA176 and partial review of TA240[5]
Key: PenTAG, Peninsula Technology Assessment Group.		

Section C: Textual clarification and additional points

We have no textual/additional queries.

References

1. National Institute for Health and Care Excellence (NICE). Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours. 2017. Available at: https://www.nice.org.uk/guidance/ta488. Accessed: 05 March 2020.
2. National Institute for Health and Care Excellence (NICE). Sunitinib for the treatment of gastrointestinal stromal tumours. 2009. Available at: https://www.nice.org.uk/guidance/ta179. Accessed: 05 March 2020.
3. National Institute for Health and Care Excellence (NICE). Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (TA86). 2004. (Updated: 01 November 2010) Available at: https://www.nice.org.uk/guidance/TA86. Accessed: 05 March 2020.
4. National Institute for Health and Care Excellence (NICE). Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2019. Available at: https://www.nice.org.uk/guidance/ta581. Accessed: 26 May 2020.
5. National Institute for Health and Care Excellence. Multiple Technology Appraisal. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer ID794. Committee papers. 2015. Available at: https://www.nice.org.uk/guidance/ta439/documents/committee-papers. Accessed: 26 May 2020.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Sarcoma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Sarcoma UK is a national charity that funds vital research, offers support for anyone affected by sarcoma cancer and campaigns for better treatments. It is the only cancer charity in the UK focusing on all types of sarcoma. It funds research into sarcoma, information and support for anyone affected by sarcoma, and campaigns for access to effective sarcoma treatments. It is entirely by fundraising.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	In early 2020, we ran the largest survey of people affected by sarcoma in the UK. It had over 1,100 responses from patients and their support networks. The survey looked across the breadth of the sarcoma landscape, from awareness of sarcoma, through diagnosis, treatment, and support. This included 87 GIST patients, 33 of whom were still undergoing active treatment. There were also 18 carers or family members of GIST patients.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	GIST is the most common type of soft tissue sarcoma; it develops in the gastrointestinal (GI) tract, a long tube running through the body from the oesophagus (gullet) to the anus (back passage) and includes the stomach and intestines. Most GISTs are found in the stomach and small bowel but can occur anywhere along the GI tract. GIST patients, on the whole, are able to live normal lives, and are able to work whilst managing side effects of treatments. However, according to their carers, almost half of the patients either often, sometimes, or always have trouble taking care of themselves. According to the National Sarcoma Survey 2020, the most common symptoms and side effects were fatigue; diarrhoea; changes to hair, skin and nails; and nausea or vomiting. GIST patients said that fatigue was the side effect with the greatest impact on their life, both during and after treatment. Sarcoma diagnosis also has a significant impact on mental wellbeing. 95% of GIST patients said that diagnosis and treatment of sarcoma negatively affected their overall mental health or emotional wellbeing.

	Caring for someone with GIST takes a large toll in many ways, including mentally, financially, and socially. Carers performed a number of tasks for the GIST patients, including providing emotional support; accompanying on trips and appointments; transporting and travelling with the patient; and communicating on behalf of the patient. Several of the respondents spent more than 50 hours a week proving care and support. As a result, well over half of the carers had to stop working or studying, either temporarily or permanently. 71% of carers said they had experienced a negative financial impact as a result of the patient's sarcoma diagnosis. Further to this, every carer (100%) said that they have felt either more often or constantly depressed or anxious since the GIST diagnosis.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are 3 main treatments available for GIST patients with metastatic and/or unresectable disease: • Imatinib • Sunitinib • Regorafenib Some treatments are more or less effective dependent on mutations within the tumour. However, there is a significant population who do not have an effective treatment either because the treatment does not target their mutation, or progression renders the treatment ineffective. Further to this, there are cases where patients stop responding to treatments. For a very small handful of patients with NTRK positive tumours, larotrectinib has just been approved for use via the Cancer Drugs Fund. Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading to many to require a lower dose.

8. Is there an unmet need for patients with this condition?	There are currently no approved therapies specifically for PDGRFA D842V-driven GIST. There are currently no lines of pharmacological therapy recommended specifically for the treatment of patients with unresectable or metastatic GIST when resistance to current therapies develops or whose disease has progressed upon treatment with third line therapy. For patients who progress through the lines of therapy mentioned above, there are no further pharmacological interventions.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients make it clear that an increased number of kinder, more effective therapies would be welcomed.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	n/a

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with a PDGRFA D842V-driven GIST will benefit most.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	n/a

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • GIST is the most common type of soft tissue sarcoma • Whilst GIST patients can, on the whole, live normal lives, side effects of treatment can be debilitating, • Treatments are regularly ineffective, particularly for those without a specific set of genetic mutations. • A new treatment for metastatic or unresectable GIST would be welcomed by patients and clinicians alike. • This is particularly true for those with PDGRFA D842V-driven GIST.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	**GIST Cancer UK** (also known as GIST Support UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**GIST Cancer UK is a registered charity (No. 1129219) formed in April 2009.** **We are a network of GIST cancer patients & carers working with top GIST specialists & National/International groups, to promote best practice. We exist to help GIST patients and their families come to terms with living with GIST cancer and we raise funds to:** • **Stimulate and fund GIST research.** • **Support Patients living with GIST cancer** • **Provide Information for GIST patients and their clinicians** • **Raise awareness of GIST cancer** **We receive no government funding and are run by a board of currently twelve volunteer trustees who have a close association and experience of GIST cancer.** **GIST Cancer UK is not a membership organisation. Each year we engage with over a thousand GIST patients and carers, both newly diagnosed and longer-term survivors, via:** • **our telephone helpline,** • **regional patient carer meetings,** • **PAWS-GIST clinics,** • **our private online patient forum** • **social media Facebook & twitter platforms** **This amounts to many thousands of patient and carer experiences since we started in 2009.**

	Each year we apply to pharma companies for grant funding to support our regional GIST patient meetings. These meetings are the bedrock of our charity from the outset, as they provide the opportunity for rare GIST cancer patients to: • **learn more about what GIST cancer is** • **learn about the latest news on GIST cancer treatments and research** • **meet and engage with other families who have been diagnosed with GIST cancer. This is very important for patients so they do not feel so isolated by this disease. Our meetings are a very practical way to offer support to patients and to provide a platform for them to also support one another.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**Yes.** **In the past 12 months GIST Cancer UK has received 2 years' worth of grant funding in one go, to help support our regional UK GIST patient meetings for 2018 & 2019.** **Blueprint Pharmaceuticals granted £12,476 to help support our patient meetings in 2018 & 2019.**

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
5. How did you gather information about the experiences of patients and carers to include in your submission?	**GIST Cancer UK has gathered information about the experiences of patients since it became a charity in 2009.** **GIST Cancer UK engages with GIST patients, clinicians and researchers both in the UK and Internationally. Our work to find answers and treatments is extensive and has resulted in the implementation of infrastructure in the UK to support and stimulate GIST research e.g. the National GIST Guidelines, establishing the National GIST Tissue Bank and also the PAWS-GIST clinic at Addenbrookes hospital in Cambridge, for even rarer subsets of GIST who currently do not have effective treatment options.** **Through our work to support GIST patients we gain valuable information about patient experiences. GIST Cancer UK engages directly with patients in a variety of ways; our private listserve (email forum community) for patients and carers, patient and carer meetings (held x3 times per year), PAWS-GIST clinics (held x3 times each year) and via our telephone helpline.** **There are some pretty horrific things that can happen in a person's life. A cancer diagnosis is one of the worst, especially if you are advised that there is no treatment, no research and no cure, it is totally devastating.** **This is what patients and their families experience. GIST is a heterogeneous cancer and there are many subtypes.** **As a result of research that happened decades ago there are some types of GIST that respond well to treatments such as Imatinib, enabling patients to live long and productive lives. If the GIST that you are diagnosed with does not have mutations that can be targeted by drugs such as Imatinib the outlook is very frightening.** **And then there is hope.**

	Hope inspired by the discovery that a new drug has been found and if you happen to be the subtype where the drug is effective then this is fantastic. Then there is the stress related to how you gain access to this new drug… **The results we have been hearing at home and abroad at conferences and directly from patients who are fortunate enough to have access to the Avapritinib drug is that it is achieving great results.** **Our patients talk to us on our private email forum and some who have first-hand experience of Avapritinib have explained their experiences to us.**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Many GIST cancer patients manage, with effective treatment, to live relatively normal lives, continuing to work and play as best they can while manging the side effects of treatment. There are some who are fortunate that their GIST cancer is found early and before it has spread, they have it removed while still small and it does not return. This is as close to a cure as currently exists.** **Depending on the extent of disease, surgery can involve quite drastic interventions such as removal of the stomach. Often the disease has reached an advanced stage prior to diagnosis, limiting the potential for surgery to totally remove the cancer. Toxic side effects are also encountered from anticancer therapies, and tolerance of these side effects varies significantly from individual to individual. Side effects to the drug therapies currently available via NHS include hypertension, hypothyroidism, debilitating hand foot syndrome, diarrhoea, fatigue, nausea, skin rashes and so on. The list of side effects is quite extensive but with advice from oncologists, cancer nurse specialists and fellow patients we observe that these can be managed and tolerated by many patients, providing the chance to live longer and live a normal life. However, some patients are forced to defer and put their lives on hold due to GIST cancer.** **Living with GIST cancer as a patient and a carer is possible but every day that you wake up you hope that it was a bad dream and that it isn't real. This is a standard defence mechanism for**

	cancer patients and their families. Learning to cope is something that you have to do and the last thing that you want to do as a carer is to give the impression that things will not be OK. You have to give your loved one hope. **The traumas and horrors of living with a type of GIST cancer that does not have a treatment that works can shatter family's lives. Carers take many forms, parents, partners, siblings, children and friends, all desperate to help and save the person that they love. A cancer diagnosis is the last thing that you think will happen to you or someone you love.**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Patients and carers are very grateful for the treatments that are available via the NHS.** **Currently for GIST patients this consists of:** • **Surgery** • **Imatinib** • **Sutent** • **Regorafenib** **Unfortunately, not all GIST cancers are the same and there are many for whom the above treatments are not effective because either their primary mutation is not targeted by the above treatments or their disease metastasizes beyond the control of the above treatments. In fact, the standard British Sarcoma Group guidelines state that:** *"If initial treatment is with imatinib, mutational analysis is particularly critical, since some GISTs are insensitive to the drug (e.g. PDGFRA exon 18 mutation D842V)".* *"There is a consensus that PDGFRA D842 V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity of this genotype to imatinib both in vitro and in vivo"*

	All GIST patients are currently given the above options but *PDGFRA* exon 18 D842v mutated GIST patients, for whom surgery is not possible, are not offered drugs because they do not work and can cause side effects. This is very alarming for them. **Avapritinib is a drug that has been designed to specifically target *PDGFRA* exon 18 mutation D842V and in addition has shown significant benefit to a host of other GIST cancer mutations where the above treatments have failed.**
8. Is there an unmet need for patients with this condition?	**Yes.** ***PDGFRA* exon 18 mutation D842V GIST patients do not currently have access to an effective targeted treatment for their type of GIST mutation via the NHS.** **For some patients with particular types of GIST, the anticancer drugs that are currently available are less / not effective. Some GIST cancer patients progress beyond the reach of Imatinib, Sutent & Regorafenib and many of those who have used Avapritinib have seen their tumours stabilise or shrink.** **The trial results we have seen for *PDGFRA* exon 18 mutated GIST indicate that 86% of patients responded and an amazing 95% experienced tumour reduction and:** • **78% (28/36) of responding PDGFRA exon 18 patients did not have disease progression as of 16 November 2018 (data cutoff), median DOR not reached** • **PFS at 12 months was 74% (95% CI, 57.7-90.2), median PFS not reached** • **OS at 12 months was 90% (95% CI, 80.0-99.3), median OS not reached** **There was also a:** • **17% overall response rate in patients without PDGFRA D842V mutations**

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**The advantages of this technology are that Avapritinib:** • **exhibits potent anti-proliferative activity in *PDGFRA* exon 18 mutation D842V GISTs and a range of other GIST mutations where the patient has progressed through currently available treatments** • **is administered orally** • **is well tolerated (most adverse events were grade 1–2)** • **use in studies has resulted in durable responses** • **rare GIST cancer patients are desperate to find drugs such as Avapritinib to shrink and stop their tumours and get their life back on track.** • **most patients were able to remain on treatment with dose modifications when needed**
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**The main disadvantage to patients currently is not having access to an effective drug.** **As with any drug there are side effects but those listed are tolerable and can be managed.** **Our understanding is that neurocognitive side effects were manageable in the majority of patients with dose interruption or reduction. In a small percentage neurocognitive side effects resulted in discontinuation.**

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**The patients who will benefit from using Avapritinib are *PDGFRA* exon 18 mutation D842V GIST patients do not currently have access to a targeted treatment for their type of GIST mutation via the NHS.** **Avapritinib will also benefit those GIST patients whose tumours progress beyond control of the currently available treatments.**
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	**No**
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- **Avapritinb is a precision medicine that targets *PDGFRA* exon 18 mutations.**
- **Trials have resulted in dramatic and durable responses for GIST patients with *PDGFRA* exon 18 mutations & other mutations out of the reach of currently available therapies.**
- ***PDGFRA* exon 18 mutated GIST patients do not have an effective treatment where surgery is not possible.**
- **Avapritinib is well tolerated (most adverse responses were grade 1-2)**
- **Using Avapritinib in GIST cancerpatients will reduce unnecessary expenditure on other ineffective therapies that are very expensive for the NHS.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Charlotte Benson**
2. Name of organisation	**Royal Marsden NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist, Sarcoma Unit**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** ☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of treatment is to halt disease progression/shrink the disease, improve progression free survival and possibly overall survival, improve symptoms, and in some cases render a patient operable with possibility of curative surgery.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Disease stabilisation or shrinkage, with concomitant improvement in disease related symptoms and prolongation of time to progression and increase in overall survival. Disease response may be seen with either change in tumour density on CT scan, or reduction in tumour dimension or both.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes- there are currently no other effective drugs available for this specific condition (PDGFRA Exon 18 D842V mutation)
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	No effective therapies are currently available for this group of patients with locally advanced/metastatic Exon 18 GIST
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: 1. Judson I, Bulusu R, Seddon B, Dangoor A, Wong N, Mudan S. UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). *Clin Sarcoma Res*. 2017;7:6. Published 2017 Apr 21. doi:10.1186/s13569-017-0072-8 2. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. 2015 Sep;26 Suppl 5:v174-7]. *Ann Oncol*. 2014;25 Suppl 3:iii21-iii26. doi:10.1093/annonc/mdu255
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, it is a clearly defined pathway Patients with GIST should be referred to expert Sarcoma centre as per NICE Improving Outcomes Guidance. Those with advanced/ metastatic disease being considered for treatment with Tyrosine kinase inhibitor (TKI) should have specialist pathology review and mutational testing performed and therefore prompt diagnosis of PDGFRA Exon 18 D842V mutation. A small group of patients may be treated outside of Sarcoma centres but this number is hopefully diminishing over time
• What impact would the technology have on the current pathway of care?	Marked improvement in outcomes for this patient group who are resistant to standard therapies for GIST
11. Will the technology be used (or is it already used) in	yes

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No change from other patients who are receiving TKI's for GIST . This is a treatment which is given as an outpatient with regular blood tests and clinical reviews at specialist centres
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Outpatient clinic in tertiary referral centre/Sarcoma Unit specialising in GIST
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No added investment to standard care
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase	Yes- early data shows significant benefit in PFS and likely OS benefit

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes- through ongoing reduction in disease burden and decrease in symptoms
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with PDGFRA Exon 18 D842V mutation (Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial [published correction appears in Lancet Oncol. 2020 Sep;21(9):e418]. *Lancet Oncol*. 2020;21(7):935-946. doi:10.1016/S1470-2045(20)30269-2) In addition a proportion of patients in the Phase I trial with more common mutations in KIT also received benefit (17%)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Monitoring of patients on avapritinib will be familiar to clinicians working in GIST. Severe adverse event rate was low in the phase I trial and no specific concomitant medications are needed over and above anti-emetics and anti- diarrhoeal agents A small proportion of patients developed neuro-cognitive side effect which clinicians and patients/carers do need to be aware of and which should be monitored.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – the usual rules will apply for patients with GIST. Careful clinical monitoring with blood tests and regular use of cross sectional imaging to assess disease response
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	From the Phase I Navigator trial , Lancet Oncology: Progression-free survival was 100% (95% CI 100–100) at 3 months, 94% (88–100) at 6 months, and 81% (69–93) at 12 months (figure 3B). As of the data cutoff, 37 (66%) of the 56 patients in the D842V population remained on treatment with a median follow-up of 15・9 months (IQR 9・2–24・9) for the overall survival analysis. Overall survival was estimated to be100% (95% CI 100–100) at 6 months, 91% (83–100) at 12 months, and 81% (67–94) at 24 months. Yes with these results I do believe there are substantial QoL benefits

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes for all the reasons noted above- previously no available therapies for this group of patients
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicities are generally mild, grade 1 and 2 Neuro cognitive effects have been noted and whilst infrequent will need to be carefully monitored as experience increases with this drug

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes- and a number of UK patients were included in the clinical trials
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Marked improvement in PFS and likely OS Significant improvement in disease status
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Neurocognitive effects will need continued monitoring

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Compassionate use programme is currently available at my institution- no new toxicities have been seen so far in the group of patients that we have treated and disease responses have been confirmed
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA86/209 (imatinib), TA179 (sunitinib) and TA488 (regorafenib)	Not relating to patients in this rare subgroup
22. How do data on real-world experience compare with the trial data?	None published but in my anecdotal data the same- drug seems well tolerated.
Equality	
23a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. What proportion of patients with unresectable or metastatic PDGFRA D842V-mutated GIST would receive each line of treatment (that is, imatinib, sunitinib, regorafenib) in NHS practice in England?	If treated according to British Sarcoma Group guidelines as noted above majority of patients with D842V mutation will not receive imatinib/sunitinib/regorafenib. However, some patients (a small proportion) with GIST are still treated outside of specialist centres or without mutational testing and so may be unsuspectingly treated along a standard paradigm. There is retrospective data from the Netherlands about a modest response rate to imatinib (2 /16 patients, 12.5%) in a small number patients with D842V and in the absence of access to avapritinib some GIST centres might try imatinib for palliative benefit but would not routinely use sunitinib/regorafenib (Farag S, Somaiah N, Choi H, et al. Clinical characteristics and treatment outcome in a large multicentre observational cohort of PDGFRA exon 18 mutated gastrointestinal stromal tumour patients. *Eur J Cancer*. 2017;76:76-83. doi:10.1016/j.ejca.2017.02.007)

Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Avapritinib is a precision medicine that targets *PDGFRA* Exon 18 mutations. • Trials have resulted in dramatic and durable responses for GIST patients with *PDGFRA* Exon 18 mutations & other mutations out of the reach of currently available therapies. • *PDGFRA* Exon 18 mutated GIST patients do not have an effective treatment where surgery is not possible. • Avapritinib is well tolerated (most adverse responses were grade 1-2) • Using Avapritinib in GIST will reduce unnecessary expenditure on other ineffective therapies	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr V Ramesh Bulusu**
2. Name of organisation	**Cambridge University Hospitals NHS Foundation Trust**

3. Job title or position	**Consultant Oncologist & Network Lead for Gastrointestinal Stromal Tumours**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X☐ a specialist in the treatment of people with this condition?** ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X☐ yes, I agree with it** ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims of the treatment are 1. Improve disease related symptoms 2. Improve progression free survival and possibly overall survival 3. Maintain and/or improve quality of life 4. Shrink tumours and slow down progression 5. In patients with borderline operable disease, to shrink the tumour and make it resectable.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In GISTs a clinically significant treatment response is measured by 1. Improvement in tumour related symptoms 2. Decrease in tumour density (as per Choi criteria) 3. Stabilisation or decrease in tumour size 4. Prolonging time to progression
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	PDGFRA D842V subset of GIST is an orphan disease with no active/effective treatment available in the metastatic/inoperable setting. Without any doubt there is a great unmet need in this subset of GISTs. Currently available tyrosine kinase inhibitors-imatinib, sunitinib and regorafenib have very limited or no activity against this subset of GISTs.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Imatinib, Sunitinib and Regorafenib—all the three tyrosine kinase inhibitors have been approved for use in metastatic/inoperable GISTs without any reference to the molecular profile/mutational status of the GIST. Currently, since no other effective treatment is available, most oncologists try one or all of these three tyrosine kinase inhibitors. Some patients may be fit enough for clinical trials-if there are any. A proportion of the patients may be offered best supportive care. Practice varies considerably both in UK, Europe and in North America.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: 1. Judson I, Bulusu R, Seddon B, Dangoor A, Wong N, Mudan S. UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). *Clin Sarcoma Res*. 2017;7:6. Published 2017 Apr 21. doi:10.1186/s13569-017-0072-8. 2. Gastrointestinal Stromal Tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2018) 29 (Suppl 4): iv68–iv78. P.G. Casali, N. Abecassis et al., on behalf of the ESMO Guidelines Committee and EURACAN.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Sarcoma & GIST clinical pathways are well defined. GISTs are treated by Sarcoma or GIST specialists in regional centres with expertise in diagnosis/pathology/radiology and surgical skills and managing patients on tyrosine kinase inhibitors. Some GISTS are still treated in smaller non specialist centres.
• What impact would the technology have on the current pathway of care?	Without any doubt this technology will change the natural history of this subtype of GIST since the currently available therapies are relatively ineffective. It is very likely that there will be significant improvements in clinical outcomes including response rates and survival of this subset of gist patients.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	The management of this subset of patients with this technology is very similar to the use of other tyrosine kinase inhibitors in GISTs. Treatment is in tablet form given as an outpatient with regular outpatient visits, blood tests, imaging and review in specialist GIST/sarcoma clinics.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In a Sarcoma/GIST specialist clinic in tertiary referral centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra investment is needed to implement this technology. We already have the expertise to manage the GIST patients treated with tyrosine kinase inhibitors.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. This technology is paradigm shifting in this subset of GISTs.

• Do you expect the technology to increase length of life more than current care?	Yes. Compared with the currently available tyrosine kinase inhibitors, this technology is very likely to improve the progression free survival and possibly overall survival.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes With significant improvement in tumour burden and disease related symptoms, we expect to observe a significant increase in quality of life compared with currently available care.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes 1. PDGFRA D842V subset of GISTs: this is where we have seen the largest clinical benefit. 2. KIT mutant GISTs in relapsed setting with a response rate of around 17% (compared with <10% with sunitinib and regorafenib)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Monitoring of patients on avapritinib will be familiar to GIST specialist teams. Severe side effects were low in the clinical trials. No extra supportive medications were needed apart from anti diarrhoeals and anti emetics as required.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	A small proportion of patients developed neuro-cognitive side effects which need careful and close monitoring and likely to require dose/schedule modifications. Healthcare professionals and patients and carers need to be trained and educated in monitoring this side effect.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No. Standard rules apply as with other GIST patients. Regular clinical review, blood tests and CT/MRI/PET CT as per present guidelines to assess response and monitor side effects.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. This is a rare subset of GIST with no clinically effective intervention. NAVIGATOR Phase I trial showed dramatic progression free survival at 6, 12 and 18 months. Progression-free survival was 100% (95% CI 100–100) at 3 months, 94% (88–100) at 6 months, and 81% (69–93) at 12 months. As of the data cut off, 37 (66%) of the 56 patients in the D842V population remained on treatment with a median follow-up of nearly 16 months. Overall survival was estimated to be100% (95% CI 100–100) at 6 months, 91% (83–100) at 12 months, and 81% (67–94) at 24 months. These results are likely to result in significant health related benefits

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, without any doubt in this rare subset of GISTS with D842V mutation in PDGFRA gene. No other standard of care to compare with. Currently available tyrosine kinase inhibitors are not very effective.
• Is the technology a 'step-change' in the management of the condition?	Yes. Most significant new intervention in this disease since the approval of imatinib over 17 years ago.
• Does the use of the technology address any particular unmet need of the patient population?	Yes In PDGFRA D842V mutant GIST patients.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most side effects are mild to moderate (grade 1 and 2) and are reversible and manageable. Neuro cognitive side effects have been observed and need careful monitoring. These may need dose and schedule interruptions or modifications.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Significant improvement in progression free survival High response and rates with reduction in tumour burden.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nothing specific. However, neurocognitive effects need careful monitoring.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Compassionate use programme for this technology has been available at our centre and we have not seen ay new or unexpected adverse events. The response rates and improvement in tumour related symptoms mirror those in clinical trials.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA86/209 (imatinib), TA179 (sunitinib) and TA488 (regorafenib)	No. Not in this subset of GISTS with PDGFRA D842V mutation.
22. How do data on real-world experience compare with the trial data?	Our early experience mirrors the clinical trial data. Drug is well tolerated.
Equality	
23a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24. What proportion of patients with unresectable or metastatic PDGFRA D842V-mutated GIST would receive each line of treatment (that is, imatinib, sunitinib, regorafenib) in NHS practice in England?	The clinical practice guidelines which have been updated 3 years ago recommend either clinical trials or supportive care for D842V mutant GISTs. However, in real life there is some data showing some benefit with Imatinib. The D842V Gists are probably heterogeneous and each patient is different. Some objective responses have been noted with imatinib in the Dutch/USA study (S Farag et al. Eur J Cancer 2017;76:76-83). In the real world in my practice I have noted slowing down of progression of disease and some objective responses.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Avapritinib is one of the best examples of precision medicine targeting the PDGFRA gene mutations in GISTs.
- Significant and dramatic responses have been observed in clinical trials.
- Durable and significant improvement in progression free survival has been noted.
- Well tolerated drug, however, requires careful clinical monitoring and should be used in specialist GIST/Sarcoma centres.
- Avapritinb is paradigm changing in the subset of GISTs with PDGFRA D842V mutation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and expert clinical advisors

None from the authors. Dr Simmonds attended a local hospital event sponsored by Novartis (manufacturer of imatinib) at which the drug ribociclib was discussed. Professor Judson declared that he had provided informal opinion to the company on some aspects of their proposed submission to NICE at the British Sarcoma Group meeting, Glasgow, in February 2020. The opinion provided is stated in the CS on pages 96, 105, 111 and 114. Professor Judson confirmed that he was not formally instructed by the company, did not provide any written evidence to the company, did not enter into any contract with the company, and did not receive any reimbursement or other incentive from the company.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report, project managed the report and is the project guarantor. Keith Cooper critically appraised the health economic systematic review, critically appraised the economic

evaluation, and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review, conducted bibliographic searches, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BNF	British National Formulary
BSC	Best supportive care
CBR	Clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CR	Complete response
CS	Company submission
CSR	Clinical study report
DoR	Duration of response
DSU	Decision Support Unit
ECG	Electrocardiogram
ECM	Established clinical management
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
EQ-5D	EuroQol 5-Dimension
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal tumour(s)
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IPW	Inverse probability weighting
ITC	Indirect treatment comparison
KM	Kaplan-Meier
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival

PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QD	Once daily (quaque die)
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SOC	Standard of care
STA	Single Technology Appraisal
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TSD	Technical Support Document
WHO	World Health Organisation

1 EXECUTIVE SUMMARY

The relevant population for this Technology Appraisal is patients who have unresectable or metastatic gastrointestinal stromal tumours (GIST) and who also have the *PDGFRA* D842V mutation. This is a very small subset of the overall GIST population, with approximately five incident cases expected in England and Wales each year. A key feature of the *PDGFRA* D842V mutation is that the tyrosine kinase inhibitors (TKIs) recommended by NICE for treating unresectable or metastatic GIST (first-line imatinib, second-line sunitinib or third-line regorafenib) are clinically ineffective in people who have this mutation.

The company submission compares the clinical effectiveness, safety, and cost-effectiveness of the intervention, avapritinib, against established clinical management (ECM), where ECM represents the use of TKIs and/or best supportive care (BSC). Given that the established TKI therapies are clinically ineffective in people with the *PDGFRA* D842V mutation, a majority of the patients in current clinical practice would be expected to receive BSC, although there may be some exceptions. Avapritinib is a new type of TKI inhibitor that inhibits *PDGFRA* D842V, thereby suppressing tumour cell proliferation, and is expected to be a first-line therapy if approved by NICE.

The company included three single-arm studies as sources of clinical effectiveness evidence for this Technology Appraisal. The Evidence Review Group (ERG) agree that these represent the best available evidence and that no relevant studies have been missed:

- NAVIGATOR: the pivotal company-sponsored prospective, single-arm, phase I/II study of avapritinib (N=56 *PDGFRA* D842V patients)
- BLU-285-1002: a company-sponsored retrospective chart review of ECM (N=19 *PDGFRA* D842V patients)
- An independent retrospective chart review study of ECM by Cassier et al (2012) which we refer to as the Cassier study (N=32 *PDGFRA* D842V patients)

In each study the relevant population of unresectable/metastatic GIST patients with the *PDGFRA* D842V mutation is a subset of a wider population of people with either unresectable/metastatic GIST (NAVIGATOR and Cassier studies) or locally advanced or unresectable/metastatic GIST (BLU-285-1002 study). NAVIGATOR is an ongoing study.

Given the lack of controlled trials, the company conducted indirect treatment comparisons (ITC) between avapritinib and ECM. An adjusted ITC was feasible for the comparison of NAVIGATOR against BLU-285-1002, i.e. adjusting for baseline imbalances in the population characteristics of the studies; but only an unadjusted (naïve) comparison was possible between NAVIGATOR and the Cassier study. The ERG agree that the overall approach to the data synthesis is appropriate.

Hazard ratios for ECM versus avapritinib from the adjusted ITC are [redacted] for overall survival (OS) and [redacted] for progression-free survival (PFS). As summarised below, and discussed in detail in this report, these results are subject to considerable uncertainty due to immaturity of the survival outcomes data (median OS was not reached), small sample sizes, inherent risks of bias, limitations in the company's studies, and limitations in the ITC methodology. However, these are currently the best data available for this technology appraisal.

A cohort partitioned survival model was developed by the company to assess the cost effectiveness of avapritinib compared to ECM. The model consists of five health states (i.e. first-line PFS, second-line PFS, third-line PFS, progressed disease, and death), and has monthly cycles and a lifetime horizon of 40 years. Patients transition to further lines of treatment according to their progression rate. Those in the avapritinib arm who progress are assumed to receive BSC and will not subsequently be treated with TKIs. Patients in the ECM arm are assumed to receive imatinib as first-line, sunitinib as second-line, and regorafenib as third-line therapy. After failing third-line therapy, patients are assumed to receive BSC (i.e. no further TKIs).

1.1 Critique of the decision problem in the company's submission

There are some minor differences between the NICE scope and company's decision problem in how ECM and BSC are described, but the ERG agree that the company's decision problem is appropriate. The key points to note are:

- Health-related quality of life (HRQoL) is specified as an outcome in the decision problem but was not assessed in the included clinical effectiveness studies (the company obtained HRQoL data for the economic model from the published literature).
- The NICE scope specifies that the company's economic analysis should include the costs of *PDGFRA* D842V mutation testing. However, the ERG believe that all

patients would be routinely tested for this mutation on diagnosis of GIST so there would be no mutation testing costs to include.

1.2 Summary of the key issues in the clinical effectiveness evidence

- There is uncertainty in the clinical treatment pathway, regarding the proportions of PDGFRA D842V patients who would receive imatinib, sunitinib, regorafenib and/or BSC. This differs between the company's clinical studies (the majority of patients received prior TKIs) and what would be expected UK clinical practice (most patients would receive BSC) (see sections 2.2.3.1 and 3.2.1.3 of this report). It is unclear whether some of this uncertainty could be resolved by wider clinical consultation or company clarification.
- Survival outcomes are immature which increases uncertainty (sections 3.2.4 and 3.2.5). This issue is not resolvable until the NAVIGATOR study is completed (or a more recent data cut provided).
- The clinical effectiveness evidence is based on small sample sizes which increases uncertainty (section 3.2.1). This issue is not resolvable unless additional data are collected – difficult due to the small number of people with the *PDGFRA* D842V mutation.
- The ECM comparators were retrospective and hence at risk of selection bias (risk of 'cherry-picking' existing data) (sections 3.2.2 and 3.4.5). This issue is not resolvable without conducting further, prospective, protocol-based, studies (or retrospective studies with random sampling and blinding) – difficult due to the small number of people with the *PDGFRA* D842V mutation.
- There is a lack of head-to-head comparative controlled studies of avapritinib versus ECM (sections 3.2.1 and 3.4.1). This issue is partly resolvable by conducting ITC analyses, albeit with uncertainties remaining due to inherent limitations in the studies and in the ITC methodology.
- Performance status score, tumour size and specific prior TKIs received could not be included as covariates in the analysis due to data limitations. It is unclear whether these would be influential as prognostic factors. This issue is not resolvable unless additional data are collected – difficult due to the small number of people with the *PDGFRA* D842V mutation.
- An adjusted ITC is not feasible for comparing the NAVIGATOR and Cassier studies due to limitations of reporting in the Cassier study; results of the alternative, unadjusted, ITC are highly uncertain (section 3.5.1). This issue might be resolvable if further data or clarification could be obtained from the Cassier study authors.

However, although the Cassier study is included in a scenario analysis (section 4.2.6), results of the unadjusted ITC do not inform the economic analysis.

- HRQoL data are lacking for people with the D842V mutation who receive avapritinib (section 3.2.5.7). This issue is partly resolvable by using HRQoL data from alternative sources (e.g. the published literature). Interim HRQoL data from a company-sponsored randomised controlled trial of avapritinib versus regorafenib (VOYAGER) are included in an ERG scenario analysis (section 6.2).

1.3 Summary of the key issues in the cost effectiveness evidence

- Whilst the model population is appropriate for the scope and the anticipated marketing authorisation, patients in the economic model are assumed to have no previous TKIs unlike those in the NAVIGATOR and BLU-285-1002 studies. Further, as noted above, the prior TKI use in these studies does not reflect the UK clinical practice. This means that there is uncertainty around the appropriateness of the modelled patient population (see sections **Error! Reference source not found.** and **Error! Reference source not found.**).
- The modelled outcomes provide a poor fit to observed OS Kaplan-Meier data for avapritinib (OS for avapritinib is overestimated). The model includes persistence of treatment benefits of avapritinib for five years with a gradual reduction of the treatment benefit over this time. Clinical experts advised the ERG that this was unlikely to be plausible and that patients who discontinue avapritinib would rapidly progress to a similar death rate as untreated patients (see section 4.2.6).
- The modelled outcomes do not provide a close fit to the observed Time on Treatment (ToT) Kaplan-Meier data for avapritinib. In addition, the ERG note that there are further inconsistencies in modelling ToT for the dose intensity of the comparator treatments. These issues produce a significant underestimate of the treatment cost for avapritinib (see section 4.2.6).
- Health utility values for first-line therapy for avapritinib and ECM appear to be implausible. The utility value used in the company's base case for patients with an initial age of [redacted] years is higher than the utility value of the general population in this age group. Clinical advice to the ERG suggests that these patients would have a lower or similar utility compared to that of the general population (see section 4.2.7).
- The survival models used, for OS and ToT, differ between treatment arms. To align with recommendations in NICE DSU TSD 14, we view it appropriate to use the same survival model for both treatment arms (see section 4.2.6).

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are shown below:

- Proportion of patients receiving TKIs in ECM assumed to be 20% imatinib, 10% sunitinib, 10% regorafenib.
- Dose intensity: Assumed the same for all TKIs.
- Duration of treatment waning: 1 month.
- Extrapolation of survival models for OS, PFS and ToT: Uses a Weibull distribution.
- Estimating ToT for avapritinib: Uses PFS as a proxy.
- All-cause mortality: Updated to ONS 2016-2018.
- Utility values for avapritinib / first-line TKI for ECM: use the general population norm.
- Resources for progressed disease: reduced resource use for patients with progressed disease (a third of patients would no longer have investigations).

The ICER using the ERG's preferred assumptions is shown in Table 1. The ICER for avapritinib versus ECM is [redacted] per QALY gained.

Table 1 ICER resulting from ERG's preferred assumptions

	Total Costs	Total QALYs	Change in costs	Change in QALYs	ICER £/QALY
Avapritinib	[redacted]	[redacted]	-	-	-
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a range of scenario analyses using our preferred assumptions as outlined below:

- Varying patients' initial age;
- Using different model time horizons;
- Varying duration of treatment waning for avapritinib;
- Including drug costs of the additional TKIs in the BLU-285-1002 study, which are not currently approved for the treatment of GIST patients in England and Wales;
- Varying the percentage of incomplete loss of treatment benefit after discontinuation for the avapritinib arm;

- Varying the post-progression rate for the avapritinib arm;
- Using alternative sources to inform model parameters such as End of Life costs, resource use, and utilities;
- Using the Cassier study as a source for comparator clinical effectiveness; and
- Assigning different survival distributions to extrapolate OS and PFS.

Results and details of these analysis are provided in section **Error! Reference source not found.**.

Across all the scenarios, the ICERs for avapritinib versus ECM remain above £50,000 per QALY. The scenarios that significantly influence the cost-effectiveness results are: using a shorter time horizon, extrapolating the OS curves using the exponential distribution, varying the duration of treatment waning for avapritinib and using the Cassier study to inform ECM clinical effectiveness. The remaining scenarios also influence the cost effectiveness results, but to a lesser extent.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Blueprint Medicines on the clinical effectiveness and cost effectiveness of avapritinib for treating gastrointestinal stromal tumours. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 12th May 2020. A response from the company via NICE was received by the ERG on 29th May 2020 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

Sections B.1.2 and B.1.3 of the company submission (CS) discuss the disease, gastrointestinal stromal tumours (GIST), the intervention (avapritinib) and its position in the treatment pathway. To support the evidence presented in the submission, the company carried out a survey of five clinicians, who are experts in the disease, to provide information on current clinical practice.[1] Of the two clinical experts advising the ERG, one agreed broadly with the opinions in the company's clinician survey whilst the other disagreed with some of the opinions, illustrating that there is uncertainty in clinical practice.

2.2.1 Background information on unresectable or metastatic gastrointestinal stromal tumours (GIST)

GIST is a type of gastrointestinal tumour that arises in the interstitial cells of the Cajal. It can occur anywhere along the gastrointestinal tract, but the most common site is the stomach.

It is possible for GISTs to be asymptomatic or silent, but where there are symptoms these may include abdominal pain, obstruction, palpable mass, upper or lower GI bleeding, anaemia, or dysphagia, and these may differ according to tumour site. The CS also lists non-specific systemic symptoms and discusses fatigue and fear in relation to the patient disease burden.

For patients presenting with localised disease surgery is expected as a cure, and only a small proportion of patients progress to or present with unresectable or metastatic disease. Patients with the *PDGFRA* D842V mutation generally have good prognosis and only around

5-6% progress to have unresectable or metastatic disease. However, when surgical resection fails, as this mutation is known to be resistant to current treatments, prognosis is the same as for any untreated patient with progressive disease.

GISTs are rare. They account for 0.1 to 3.0% of all gastrointestinal malignancies.[2] The most recent UK prevalence study estimates a prevalence of third-line treatment-eligible GIST of 1/100,000 and a prevalence count of 598.[3] This is similar to the European studies which estimate an incidence of 1 to 1.5/100,000 per year of GIST.[4,5] There are an estimated 650 new cases per year in the UK, 900 in total, and the median age at diagnosis is 60 to 65 years but the range is wide.[6]

The CS estimates that in England and Wales there are 30-40 patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation, with about 5 new cases per year.

2.2.2 Background information on avapritinib

- CS Table 2 presents information on avapritinib.

- Avapritinib is a Type 1 tyrosine kinase inhibitor (TKI) that has been shown in vitro to inhibit activity of several *PDGFRA* exon 18 mutants and several KIT exon 11, 11/17 and 17 mutants. The *PDGFRA* D842V mutation is the most common of the exon 18 mutations, and patients with this mutational status are the population of interest for this submission.

- Avapritinib was granted an EMA orphan drug designation for the treatment of GIST in August 2017;[7] [redacted]. Avapritinib received an FDA fast track and orphan drug designation and was granted FDA approval for the treatment of adults with unresectable or metastatic GIST harbouring a *PDGFRA* exon 18 mutation (including D842V) in January 2020.[8]

- The intended licensed dosage is 300mg once daily, taken orally, until disease progression or unacceptable toxicity.

2.2.3 The position of avapritinib in the treatment pathway

2.2.3.1 Current treatment pathway

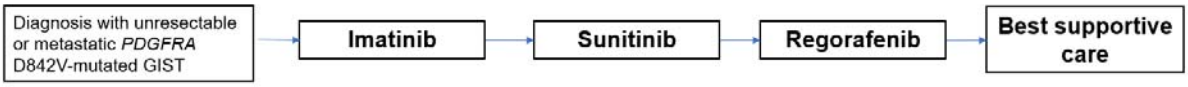
The CS outlines three current clinical guidelines for the treatment of GIST: The British Sarcoma Group for UK guidelines,[6] ESMO European guidelines,[9] and The National Comprehensive Cancer Network guidelines for the USA.[10] The ERG's clinical experts both

indicated that the guidelines most used in England are the UK (BSG) and European (ESMO) guidelines which are similar, with the BSG ones adapted to reflect UK drug availability.

On disease progression, NICE guidance approves sequential administration of the TKIs imatinib, sunitinib and regorafenib as first-, second- and third-line treatments respectively for unresectable or metastatic GIST.[11-13] Patients with the *PDGFRA* D842V mutation are known to be resistant to treatment with existing TKIs.[14,15] This is acknowledged in the guidelines; however, neither the NICE guidance, nor the clinical guidelines provide recommendations for treating unresectable or metastatic GIST in patients with the *PDGFRA* D842V mutation, as currently no known effective treatment is available. The clinical guidelines only say that patients failing on treatment can be considered for inclusion in clinical trials of new agents. Therefore, in UK clinical practice, it is not certain that patients with unresectable or metastatic GIST who have the *PDGFRA* D842V mutation would be treated with all three TKIs sequentially.

The company's view of the clinical pathway for patients with the *PDGFRA* D842V mutation, as used in the economic model, does not differ from the UK clinical pathway for the general unresectable or metastatic GIST population (CS section B.1.3.3.2). It is reproduced in Reproduced from CS Figure 1

Figure 1 below.



Reproduced from CS Figure 1

Figure 1 Company view of the current clinical pathway for patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation

The company refer to the use of TKIs (imatinib, sunitinib, regorafenib) and/or best supportive care (BSC) together as comprising "established clinical management" (ECM) in their decision problem (see section 2.3 below). The company do not explicitly define BSC. According to the ERG's clinical experts, BSC could include non-drug therapy such as surgery or ablation for specific lesions, with palliative intent.

According to the ERG's clinical experts, the company's clinical pathway for people who have unresectable or metastatic GIST and who have the *PDGFRA* D842V mutation is not reflective of UK clinical practice for the following reasons:

- Since imatinib, sunitinib and regorafenib lack clinical effectiveness among patients with the PFGFRA D842V mutation and carry a toxicity burden they would not usually be prescribed for this subgroup (in the company's clinician survey only two out of five clinicians responded that they would treat these patients with TKIs[1]).

- Patients with the *PDGFRA* D842V mutation might have received imatinib before their mutational diagnosis is known, for which they could wait up to three or four weeks. Most would discontinue imatinib once confirmed to have the *PDGFRA* D842V mutation.

- Among those patients who do receive imatinib, very few, if any, would subsequently receive sunitinib or regorafenib, due to lack of effectiveness and risk of toxicity.

In summary, whilst we agree that ECM (comprising TKIs and/or BSC) is an appropriate comparator, we disagree that the relative balance of TKIs and BSC in the company's clinical pathway reflects UK practice. Patients with the *PDGFRA* D842V mutation in UK clinical practice would predominantly receive BSC, with relatively few receiving imatinib and very few if any would go on to receive sunitinib or regorafenib. However, the clinical experts acknowledged that there is likely to be considerable variation in practice.

We note that whilst the whilst company's clinical pathway does not align with expected UK clinical practice, it does align with the company's studies, in which some patients with the *PDGFRA* D842V mutation received all three TKIs (imatinib, sunitinib, regorafenib). This is discussed further in section 3.2.1.3 below.

2.2.3.2 Treatment pathway with avapritinib

It is expected that, since the *PDGFRA* D842V mutation is resistant to other TKIs, avapritinib will be the first line of treatment after diagnosis with unresectable or metastatic disease and confirmation of mutational status.

There remains the possibility that a patient may have been receiving imatinib first line whilst waiting for the results of mutational diagnosis which can take up to three to four weeks from testing. In these cases, imatinib would be discontinued on confirmation of a D842V mutation and avapritinib would be given.

After failing to respond to avapritinib patients would receive BSC (CS section B.3.2.4).

ERG conclusion

- The ERG do not agree that the current clinical pathway, as represented in CS Figure 1, is representative of UK clinical practice for patients who have the *PDGFRA* D842V mutation.
- However, there is uncertainty around the use of TKIs for patients who have the *PDGFRA* mutation. Clinical experts consulted by both the company and the ERG had differing views around giving patients ineffective but toxic treatment (also at high monetary cost).

2.3 Critique of the company's definition of the decision problem

Error! Reference source not found. summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the ERG's comments on this.

The company's decision problem is broadly consistent with the NICE scope, but the following points should be noted:

- The NICE scope and decision problem give different definitions of ECM (see Table 2). The NICE scope definition of ECM includes BSC but does not appear to include the TKIs (imatinib, sunitinib and regorafenib). However, the company's decision problem defines ECM as including the TKIs and BSC. We agree that the company's definitions of the comparators are appropriate and reflect how ECM is modelled in the economic analysis (see section 4.2.2). (NB: as discussed in section 2.2.3 above, whilst ECM is appropriate as an overall comparator, the relative balance of TKIs and BSC differs between the company's ECM pathway and that which would be expected in UK clinical practice.)
- The NICE scope specifies that the company should include the costs of *PDGFRA* D842V mutation testing in their economic analysis. However, mutational testing for *PDGFRA* D842V is done routinely on diagnosis of GIST, meaning that there are no additional mutation testing costs relevant to avapritinib that would need to be included.

Table 2 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (*PDGFRA*)	[redacted].	This is the population for which avapritinib is anticipated to receive its marketing authorisation	The decision problem population matches the NICE scope and the intended licensed

	D842V mutation regardless of prior therapy.		from the EMA and is in line with the evidence presented in the pivotal NAVIGATOR study.	indication and is consistent with the *PDGFRA* D842V mutation subgroup in the pivotal NAVIGATOR study.
Intervention	Avapritinib	Avapritinib	Not applicable	Not applicable
Comparators	• Imatinib (for adults who have KIT [CD117]-positive tumours) • Sunitinib (for adults whose treatment with imatinib has failed due to resistance or intolerance) • Regorafenib (for adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib) • Established clinical management without avapritinib including best supportive care	Established clinical management without avapritinib including: • Imatinib • Sunitinib (for adults whose treatment with imatinib has failed due to resistance or intolerance) • Regorafenib (for adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib) • Best supportive care	The appropriate comparators have been selected for the anticipated licensed population for avapritinib in line with clinical opinion.	The comparators are worded differently in the NICE scope and decision problem. However, we agree with the company's definition of the comparators which aligns with how ECM is modelled in their economic analysis (an ECM comparator arm includes imatinib, sunitinib, regorafenib and BSC).

Outcomes	The outcome measures to be considered include: • Overall survival • Response rate (including partial response rate and duration of response) • Progression-free survival • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Response rate (including partial response rate and duration of response) • Progression-free survival • Adverse effects of treatment • Health-related quality of life • Time on treatment	Time on treatment is an important outcome of interest for use in the economic model, as tracking patient outcomes via line of therapy avoids the issue of noncomparability of progression across treatments	All outcomes in the NICE scope are included in the decision problem. We note that health-related quality of life (HRQoL) was not assessed in the pivotal avapritinib study and the company have sourced HRQoL data in their economic analysis from other sources (section 4.2.7). The additional inclusion of time on treatment in the decision problem is appropriate, as this outcome informs the economic model.
Economic analysis	• The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	• The cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year	According to clinical experts [company's expert opinion survey], nearly all patients will have their mutational status known before or within three	The company's assumption that all GIST patients would be routinely tested for the *PDGFRA* D842V mutation in clinical practice is appropriate.

	• The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account • The use of avapritinib is conditional on the presence of the *PDGFRA* D842V mutation. The economic modelling should include	• The time horizon runs until over 99% of patients have died in both treatment arms • Costs are considered from an NHS and Personal Social Services perspective • Where known, commercial arrangements for the intervention, comparator and subsequent treatment technologies are taken into account • The clinical evidence is based only on eligible (i.e. metastatic or unresectable) patients with the *PDGFRA* D842V mutation	weeks of diagnosis with unresectable or metastatic GIST.	Routine *PDGFRA* D842V mutation testing is recommended by the relevant UK guidelines (the British Sarcoma Group guidelines say that "mutational testing is obligatory" in GIST [6]) and the ERG's clinical advisors agreed that all GIST patients would be routinely tested for this mutation on diagnosis. There are therefore no additional mutation testing costs relevant to avapritinib that would need to be included.

	the costs associated with diagnostic testing for the *PDGFRA* D842V mutation in people with unresectable or metastatic GIST who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals			
Subgroups	Not applicable	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Not applicable	Not applicable	Not applicable	Not applicable
Source: CS Table 1				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of the company's systematic literature review

The systematic literature review performed by the company is reported in CS Appendix D, and the ERG's assessment of the review is summarised in Table 3 below. Overall the company's review is fit for purpose and we believe all relevant studies have been identified. However, we disagree with the company's risk of bias assessment approach, as explained in section 3.2.2 and Appendix 2 in this report.

Table 3 ERG appraisal of systematic review methods

Systematic review components and processes	ERG response	ERG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The PICOS (S=study type) is defined in Appendix Table 5 for the eligibility criteria. It matches the decision problem.
Searches: was the literature review carried out appropriately (sources, date range, in line with PICOD, correct search terms/syntax, etc.)?	Yes	Reported in CS Appendix D.1 See Appendix 3 for detailed ERG comments.
Searches: were any relevant studies missed?	No	The identified studies are listed in CS Appendix Tables 13 and 14. The ERG and our clinical experts are not aware of any missing studies.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes Yes	CS Appendix Table 5.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix D.1 page 19 Two independent reviewers for both level 1 and 2 screening, with disagreements checked by a third reviewer.

Was data extraction performed to a reasonable standard (e.g. use of two reviewers)?	Yes	CS Appendix D.1 page 19 Data extraction was performed by one researcher and verified against the original source by a second researcher.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Downs and Black checklist.[16] CS Appendix D.3 and CS Appendix Table 19. Discussed in section 3.2.2 and Appendix 2 in this report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Yes	Not reported but clarified by company at factual error check stage (NB ERG disagree with company approach to risk of bias assessment – see section 3.2.2)
Is sufficient detail on the individual studies presented?	Partly	CS Tables 14 and 15 and CS Appendix Tables 14 and 15 (baseline characteristics). Limited data for BLU-285-1002 are given in the CS, so ERG have sourced these from the CSR.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	See section 3.4 of this report

3.1.1 ERG summary of the company's literature searches

The company performed a sensitive search of the literature including all relevant and recommended sources. The search included terms for all approved or investigational pharmacological interventions used to treat GIST except that there were no terms used to express BSC and, therefore, the search may have missed any BSC-only studies. By the time of receipt of the CS the searches were over five months out of date. We therefore ran updated searches in Medline, Embase and the Cochrane Library, and checked Medline for any BSC-only studies with no date limit. We found no further relevant studies. The ERG is satisfied that the review was carried out to a good standard, albeit with some lack of clarity of reporting, and that it was appropriate to this appraisal. For reference, detailed ERG comments on the searches are given in Appendix 3.

3.2 ERG critique of the included clinical effectiveness studies

3.2.1 Included studies

The company's systematic literature search and study selection process identified the following seven studies relevant to the decision problem. All of these studies except BLU-285-1002 included a mix of GIST patients with and without the *PDGFRA* D842V mutation, meaning that the *PDGFRA* D428V population relevant to the current appraisal is a subgroup from each study (except BLU-285-1002). As a consequence, sample sizes (N) are small (only 3 to 12 patients in four studies), with the largest *PDGFRA* D842V subgroup sizes being in the NAVIGATOR, BLU-285-1002 and Cassier studies (22 to 56 patients):

- NAVIGATOR; a company-sponsored multinational single arm prospective study on avapritinib (N=56)[17-21]
- BLU-285-1002: a company-sponsored retrospective chart review of patients at three centres in the USA who had received imatinib, sunitinib and regorafenib (N=22)[22,23]
- Cassier et al. 2012: an international survey of GIST referral centres on patients who had received imatinib first-line and sunitinib (N=32)[24,25]
- Rutkowski et al. 2012: a retrospective single-centre registry of Polish GIST patients who had received sunitinib (N=12)[26]
- Yoo et al. 2016: a retrospective single-centre registry of Korean GIST patients who had received imatinib and sunitinib (N=9)[27]
- Osuch et al. 2014: a retrospective multi-centre registry of Polish GIST patients who received imatinib (N=8)[28]
- B222: a multi-centre randomised controlled trial (RCT) of GIST patients who received two doses of imatinib (N=3)[29]

The NAVIGATOR, BLU-285-1002 and Cassier studies contribute to the company's economic analysis as follows:

- NAVIGATOR (avapritinib) and BLU-285-1002 (ECM) were compared in an adjusted indirect treatment comparison (ITC) which informs the company's economic model base case.
- NAVIGATOR (avapritinib) and the Cassier study (ECM) were compared in an unadjusted ITC (CS Appendix Table 15 and Appendix P), with the survival outcomes informing a scenario analysis (CS section B.3.8.3).

We have therefore focused the current report on the characteristics and results of the NAVIGATOR, BLU-285-1002 and Cassier studies. The remaining four studies (B222, Rutkowski, Osuch, Yoo) are discussed narratively by the company (CS Appendix Tables 13, 14, 16, 17 and accompanying text) and the B222 trial was considered by the company as a potential source of health utility data (as noted in section 4.2.7 below). These four studies do not inform the economic model and are not discussed further in this report because they are limited by their very small sample sizes (and none included any UK patients), among other limitations which are summarised in CS Table 14.

Ongoing studies

The NAVIGATOR study is currently ongoing, with incomplete follow-up of survival outcomes. Study outcomes are reported for two interim data cuts (see Table 4 below). The company advised in clarification response A1 that the final CSR for NAVIGATOR will not be available until [redacted].

One other relevant ongoing study, VOYAGER, was identified by the company (CS section B.2.11). This is an open-label company-sponsored RCT comparing avapritinib against regorafenib in patients with locally advanced, unresectable or metastatic GIST previously treated with imatinib and one or two other TKIs. The numbers enrolled are not clearly reported. VOYAGER includes a subgroup of patients with the *PDGFRA* D842V mutation, but only 12 of these patients have been recruited (six in each treatment group). The company confirmed in clarification response A1 that a CSR for VOYAGER is not currently available ([redacted]). However, on request from the ERG (clarification question B6) the company provided HRQoL data from VOYAGER for inclusion in an ERG scenario analysis (see section 6.2). These HRQoL data were the only VOYAGER outcomes available for the ERG to consider at the time of preparation of this report.

The ERG searches did not identify any other ongoing studies of avapritinib or the comparators in the decision problem that would be completed within the timeframe of the current appraisal. Ongoing studies that we are aware of are:

- INVICTUS (RCT: ripretinib versus placebo) is expected to complete in December 2020. This trial only has 3 *PGDFRA* D842V patients.
- INTRIGUE (RCT: ripretinib versus sunitinib) is not due to complete until March 2022. No data have been published yet. It is unclear how many *PDGFRA* D842V patients have been enrolled so far.

3.2.1.1 Study characteristics

Characteristics of the three key studies are summarised in Table 4. Few details of BLU-285-1002 are reported in the CS and so we have sourced these from the CSR. The NAVIGATOR study was conducted prospectively whilst both the comparator studies retrospectively collated patient data from clinical records.

The NAVIGATOR study included patients who received a range of daily doses of avapritinib (30mg, 60mg, 90mg, 135mg, 200mg, 300mg, 400mg, 600mg) and the company's analyses of clinical effectiveness outcomes are based on the "all doses" pooled group to maximise the available sample size (N=56). The analysis population therefore included [redacted] patients ([redacted]%) who had received the intended licensed indication dose of 300mg, [redacted] patients ([redacted]%) who had received lower doses, and [redacted] patients ([redacted]%) who had received higher doses. Clinical experts advising the ERG consider that the company's dose pooling approach is appropriate. This is based on experience with other TKIs that suggests clinical effectiveness outcomes would be unlikely to differ markedly across the included doses, with one expert commenting that dose pooling to increase the sample size is a standard practice in phase I/II studies. The company have provided data separately for the 300mg, 400mg and all-doses groups (but not the lower-dose groups) for baseline characteristics and effectiveness outcomes (CS Appendix L) and for safety outcomes (CS Appendix F). We consider the homogeneity of these dose groups in relation to patients' baseline characteristics (see below); clinical effectiveness outcomes (see section 3.2.5) and safety outcomes (see section 3.3).

The BLU-285-1002 study was designed to serve as a "historical control for efficacy studies of avapritinib" (CS section B.2.9). However, in BLU-285-1002 most patients had initially received adjuvant TKI therapy for locally advanced GIST, which has a different prognosis to the decision problem population, i.e. people with unresectable or metastatic disease. To enable a comparison of BLU-285-1002 against NAVIGATOR, the company reviewed the records of patients in BLU-285-1002 to separate the TKI use that had been received in the adjuvant setting from the TKI use that had been received for unresectable or metastatic disease. The company did this by identifying the first TKI that each patient had received for unresectable or metastatic disease and then including only the patient's data from that point onwards in analyses. This approach enabled 19 of the 22 patients in BLU-285-1002 to be included in comparisons against the NAVIGATOR study.

The Cassier study included 32 patients with unresectable or metastatic GIST who had the *PDGFRA* D842V mutation and can be compared with the NAVIGATOR study population. As discussed further below, a limitation of the Cassier study is that patients' baseline characteristics are reported for the whole study group, not specifically for those with the *PDGFRA* D842V mutation.

Table 4 Overview of the intervention and comparator studies

	Study		
Study feature	**NAVIGATOR**	**BLU-285-1002**	**Cassier et al 2012**
Study design	Prospective, single arm phase I/II study	Retrospective chart review	Retrospective chart review
Status	Ongoing, unpublished	Complete, unpublished	Complete, published
Study population	[redacted]	[redacted]	Adults who had *PDGFRA* mutant advanced or metastatic GIST and had been treated with imatinib in a non-adjuvant setting
Number and location of centres/ data sources	[redacted]	[redacted]	12 European centres plus 2 EORTC clinical trials
Total study population	[redacted]	[redacted]	N=58
Number with the *PDGFRA* D842V mutation	N=56 [redacted]	[redacted]	N=32
Number of UK patients	[redacted]	[redacted]	Not reported whether any UK centres were included
TKI dosing regimens included	[redacted]	[redacted]	Imatinib 400mg QD (n=44) 800mg QD (n=14)
Primary analysis group used for the current appraisal	[redacted] (N=56)	[redacted] (N=19)	*PDGFRA* D842V mutation subgroup (N=32)
Outcomes	[redacted]	[redacted]	Response (CR, PR, SD, PD); OS; PFS
Latest available data	[redacted]	[redacted]	Date of starting imatinib ranged from January 2001 to November 2010
Median duration of follow-up	[redacted]	[redacted]	45.3 months

Source: CS for NAVIGATOR data; CSR for BLU-285-1002 data; Cassier study data from study publication.

CBR: clinical benefit rate; CR: complete response; CSR: clinical study report; DoR: duration of response; EORTC: European Organisation for Research and Treatment of Cancer; KM: Kaplan-Meier; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; QD: once daily; SD: stable disease; TKI: tyrosine kinase inhibitor; ToT: time on treatment

3.2.1.2 Patients' baseline characteristics

The baseline characteristics of the three key studies are summarised in Table 5. The population characteristics for the BLU-285-1002 and Cassier studies are incompletely reported in the CS and we have therefore sourced these from the CSR[22] and study publication[25] respectively. Some of the characteristics shown in Table 5 were considered by the company to be potential prognostic factors and were adjusted for in the company's indirect comparison between the NAVIGATOR and BLU-285-1002 studies (for discussion of the ITC see sections 3.4 and 3.5).

When comparing the baseline characteristics between the studies it should be borne in mind that the characteristics reported for NAVIGATOR and BLU-285-1002 are for people with the *PDGFRA* D842V mutation whereas the characteristics in the Cassier study are reported for the whole study population, i.e. people with and without the mutation. In the Cassier study just over half of the patients (32/58; 55%) had the *PDGFRA* D842V mutation. Clinical experts advising the ERG suggested that baseline characteristics would be unlikely to differ between people with unresectable or metastatic GIST with or without the PGDFRA D842V mutation. However, the ERG are concerned that differences in TKI use might be expected but this is unclear in the Cassier study due to lack of reporting of patients' baseline characteristics for the mutation subgroup.

Clinical experts advising the ERG agreed that the characteristics of participants in the comparator studies would be similar to those expected in UK clinical practice, with the following exceptions:

- A key feature of participants in NAVIGATOR and BLU-285-1002 is that they received a higher frequency of prior TKIs than would be expected in UK clinical practice (discussed further below – see section 3.2.1.3).
- Participants in the NAVIGATOR and Cassier studies had relatively low ECOG/WHO performance status scores (almost all PS=0 or PS=1) so would have had better performance status than would be expected in clinical practice. Performance status is uncertain for the BLU-285-1002 study due to the majority of data being missing.

- One of the clinical experts advising the ERG commented that the sex distribution of patients, with more than half (range 59% to 70%) being male in each study, is atypical of clinical practice, where a more balanced sex ratio would be expected. The explanation for this difference is unclear but sex is not known to be a prognostic factor and so we believe that the imbalance would not influence effectiveness or safety results. In an analysis of the NAVIGATOR data by the US FDA,[30] sex did not appear to influence treatment outcomes, although firm conclusions are hindered by the small sample size.

Table 5 Patient baseline characteristics in the intervention and comparator studies

Study		**NAVIGATOR**	**BLU-285-1002**	**Cassier et al 2012**
Intervention Population group **Baseline characteristics**		**Avapritinib** All doses group [a] (N = 56)	**Imatinib** Participants receiving their first TKI for unresectable or metastatic disease (N=19)	**Imatinib** Full study population (not limited to *PDGFRA* D842V mutation group) (N=58)
Sex, n (%)	Male	[redacted]	[redacted]	34 (59)
	Female	[redacted]	[redacted]	24 (41)
Age, years, n (%)	< 60	[redacted]	[redacted]	Not reported
	≥ 60	[redacted]	[redacted]	Not reported
Age, years, median (range)		[redacted]	[redacted]	61 (19–83)
Race, n (%)	White	[redacted]	[redacted]	Not reported
	Non-white	[redacted]	[redacted]	Not reported
	Missing	[redacted]	[redacted]	Not reported
Region	US	[redacted]	[redacted]	0
	Europe	[redacted]	[redacted]	58 (100)
	Asia	[redacted]	[redacted]	0
Anatomical site, n (%)	Gastric (stomach)	[redacted]	[redacted]	40 (69)
	Other	[redacted]	[redacted]	18 (31)
Metastatic disease, n (%)		[redacted]	[redacted]	56 (97)
ECOG/WHO performance status, n (%)	0	[redacted]	[redacted]	28 (48)
	1	[redacted]	[redacted]	19 (33)
	2	Not reported	Not reported	2 (3)

	2+	[redacted]	[redacted]	Not reported
	Missing	[redacted]	[redacted]	9 (16)
Duration of disease, n (%)	< 3 years	[redacted]	[redacted]	Not reported
	≥ 3 years	[redacted]	[redacted]	Not reported
Total number of TKI, n (%)	1	[redacted]	[redacted]	29 (50) [e]
	2	[redacted]	[redacted]	21 (36) [e]
	3	[redacted]	[redacted]	5 (9) [e]
	4+	[redacted]	[redacted]	0 [e]
	Unclear	[redacted]	[redacted]	3 (5) [e]
Prior imatinib, n (%)		[redacted]	See footnote [f]	15 (26) [e]
Prior sunitinib, n (%)		[redacted]	See footnote [f]	18 (31) [e]
Prior regorafenib, n (%)		[redacted]	See footnote [f]	0 [e]
Largest target lesion/ primary tumour size by n (%)	≤ 5 cm	[redacted]	See footnote [h]	Not reported
	> 5 to ≤ 10 cm	[redacted]	See footnote [h]	Not reported
	> 10 cm	[redacted]	See footnote [h]	Not reported
	missing	[redacted]	See footnote [h]	Not reported
Other baseline characteristics which are reported in the CS and/or study publication but are not extracted here		[redacted] (CS Table 7 and CSR)	[redacted]	NIH risk group; Miettinen risk group; site of metastatic disease; median tumour size; mitotic rate (Cassier study paper)

Source: CS Tables 7 and 15; CS Appendix Table 14; BLU-285-1002 CSR; [22] Cassier study publication[25]
[a] includes patients with < 300 mg QD and 600 mg QD starting dose.
[b] error in denominator for % in CS Table 15 and ITC report;[31] corrected by ERG
[c] incorrectly reported in CS Appendix Table 14 as 68%
[d] Note these ECOG performance status data are unreliable due to 18/19 (95%) missing
[e] calculated by ERG based on data reported in the text of the study publication (see Appendix 1)
[f] reported in CSR Table 8, but only for the full study population (N=22), therefore would include adjuvant therapy for locally advanced disease so not relevant to the current appraisal. Also reported in CSR Tables 14.1.1.7B and 14.1.1.7C for the unresectable/metastatic GIST group (N=19) but only as partial data that are not comparable with those from NAVIGATOR.
[g] refers to size of the "target lesion" by central radiological assessment
[h] data on the size of the "primary tumour" are reported in the CSR but are for the full study population (N=22) and therefore may not be reflective of tumour size specifically in unresectable or metastatic GIST patients

The company present baseline characteristics for the NAVIGATOR population separately for the 300mg and 400mg dose groups (but not the lower-dose groups) in CS Appendix L (not reproduced here). Due to the relatively small sample sizes it is difficult to draw any firm conclusions about whether the baseline characteristics differ systematically between the

300mg (N=[redacted]), 400mg (N=[redacted]) and all-doses (N=56) groups, but no substantive differences are evident (CS Appendix Table 50).

3.2.1.3 Prior TKI use in the included studies

The frequency of prior imatinib, sunitinib and regorafenib use (Table 5) was higher in the NAVIGATOR study than would be expected in UK clinical practice (see section 2.2.3.1 above). The CS does not explain why patients with the PDGFRA D842V mutation in the NAVIGATOR study received prior TKIs.

Prior TKI use in the BLU-285-1002 study is only reported in the CSR and was also higher than would be expected in UK clinical practice; however, the data are for the full study population (N=22) so presumably include TKI use in the locally advanced GIST setting which would not be relevant to the current appraisal (Table 5).

Baseline characteristics in the Cassier study, including prior TKI use, are reported only for the overall unresectable/metastatic GIST population, not specifically the *PDGFRA* D842V subgroup. Although clinical experts advising the ERG suggested that these two populations would not be expected to differ on baseline characteristics, we are uncertain whether that would apply to prior TKI use which, theoretically, should be different between these populations given that the TKIs are not clinically effective in the *PDGFRA* D842V subgroup.

Clinical experts advising the ERG agreed that the following explanations for the difference in prior TKI use between the avapritinib and ECM studies and UK clinical practice would be plausible:

- Both company studies included US centres (8/19 in NAVIGATOR, 3/3 in BLU-285-1002) which may not be reflective of UK TKI use due to major differences in the US and UK healthcare systems (e.g. US oncologists could receive financial benefits for prescribing ineffective and expensive treatments).
- Patients may have commenced imatinib per standard therapy for unresectable metastatic GIST while awaiting their *PDGFRA* D842V mutation test result. Although patients would usually discontinue imatinib when the *PDGFRA* D842V mutation is confirmed, some might be continued on imatinib for symptom (e.g. pain) control. The CS does not report the time to mutation test results nor the proportion of patients who received late test results in the company studies. Clinical experts advising the ERG noted that mutational status may not be standardised across countries.

- Due to the small size of the *PDGFRA* D842V subgroup and relative lack of clinical experience in treating these patients, clinicians may be heterogeneous in the therapy they provide, perhaps prescribing TKIs due to this being "better than doing nothing". The ERG's clinical experts noted that TKI administration might be based on anecdotal evidence (e.g. a case report of regorafenib benefit in a single patient).

The above explanations, whilst speculative, are indicative of where there are uncertainties in clinical practice. The CS does not explicitly state whether any prior TKIs administered before patients enrolled in the NAVIGATOR study had been employed in the adjuvant setting (i.e. prior to unresectable or metastatic disease diagnosis). However, we believe this to be unlikely since: (i) There is a consensus that *PDGFRA* D842V-mutated GISTs should not be treated with any adjuvant therapy[6] and our clinical expert advisors concurred. (ii) The company had excluded adjuvant TKI use in their analysis of BLU-285-1002 and presumably would have done the same for NAVIGATOR had any of the enrolled patients been known to have received prior TKIs in an adjuvant setting.

ERG conclusion

One single-arm prospective study on avapritinib and two retrospective chart review/survey studies on comparator TKIs (i.e. ECM) are relevant to this appraisal. The populations available for analysis have relatively small sample sizes (N=19 to N=58). The participants in the avapritinib study received more frequent prior TKI use than would be expected in UK clinical practice, despite TKIs being ineffective in the *PDGFRA* D842V subgroup. The TKI use in the ECM studies is unclear as it was not reported for the relevant subgroup of patients who had unresectable/metastatic GIST and the *PDGFRA* D842V mutation. The rationale for why patients with the *PDGFRA* D842V mutation group in these studies received TKIs is not discussed.

3.2.2 Risk of bias assessment

The company assessed the avapritinib and comparator studies using the Downs and Black checklist for non-randomised studies.[16] This checklist contains 27 questions which assess four aspects (domains) of study quality: reporting, internal validity (bias and confounding), power, and external validity. The checklist has been validated by its authors for internal consistency, test-retest and inter-rater reliability, and criterion validity [16] and evaluated independently.[32] We are unclear how frequently the Downs and Black checklist has been used for evaluating non-randomised studies in NICE Technology Appraisals.

The company report results of the assessment as yes/no answers to each question in CS Appendix Table 19. One question about power has not been answered (question 27) (see section 3.2.4 for discussion of statistical power). As noted by Deeks et al. in a review of quality assessment tools,[32] most of the questions in the Downs and Black checklist relate to reporting rather than validity. We have therefore focused on those questions concerning internal validity (bias and confounding) (questions 14 to 26) for the present appraisal.

A comparison of the company's and ERG's assessments of the NAVIGATOR, BLU-285-1002 and Cassier studies for questions 14 to 26 of the Downs and Black checklist is shown in Appendix 2. However, we encountered several problems whilst applying the checklist to the included studies, as explained in Appendix 2.

The key issues identified from the ERG's validity assessment, which apply to all the measured outcomes, are:

- The studies were all single-arm studies which may be at risk of bias (selection bias, performance bias, and/or confounding) since factors other than the intended intervention might explain the outcome (such factors can be controlled for in comparative studies but not in single-arm studies).
- The comparator studies were retrospective chart reviews which carries an additional risk of selection bias arising through the possibility of selective ascertainment (i.e. "cherry picking") of cases and/or results.
- The studies had relatively small sample sizes. Whilst small sample sizes may not necessarily introduce bias (i.e. systematic error) they would increase uncertainty in estimates of effects through lack of precision.

An appropriate way to reduce the risk of selection bias in the evidence synthesis would be to ensure that active treatment and comparator groups of the single-arm studies are as well-matched as possible on participant characteristics when conducting an indirect treatment comparison (ITC). We assessed the risks of bias in the company's approach to their ITC, as described in section 3.4.5 below.

ERG conclusion

The included studies are inherently at risk of bias due to their single-arm designs and, in the case of the comparator studies, their retrospective designs.

3.2.3 Outcomes assessment

The CS provides information for the outcomes of the NAVIGATOR study across CS Tables 4, 5, 6 and 8. All outcomes specified in the scope and decision problem, except for HRQoL, are reported.

Appendix 4 of this report provides further description of the primary, secondary and exploratory outcomes of the NAVIGATOR study that are reported in the CS.

The CS uses outcomes commonly reported in cancer drug appraisals: overall response rate (ORR), overall survival (OS), progression-free survival (PFS), duration of response (DoR), disease control rate (DCR) and clinical benefit rate (CBR). Additional time to event endpoints that have been used are Time to Response and Time on Treatment (ToT) (for definitions see Appendix 4). PFS can be used as a surrogate for OS, yet neither PFS nor OS data are mature in the NAVIGATOR study. Therefore, ORR is appropriate as the primary outcome (supported by DoR as a secondary outcome), in the NAVIGATOR study. ORR is useful for clinical effectiveness assessment in single-arm trials where there is no available therapy, requires a smaller population, and can be assessed earlier than overall survival data.[33,34]

Table 6 in the CS reports that the outcomes are based on tumour status assessed centrally, with measurements for ORR, DoR, PFS, and CBR based on the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 which is a standard for measuring treatment response based on tumour shrinkage. According to the CSR, in order to minimise bias, assessment of the primary outcome (i.e. ORR) was carried out by two independent reviewers concurrently who were blinded to the results of the other reviewer, when adjudication was performed the third reviewer was blinded to the identities of the first two reviewers but not to their analyses.

The following outcomes inform the economic model. These are based on the most recent January 2020 data cut, except for adverse effects of treatment which are based on the November 2018 data cut:

- Adverse effects of treatment, primary outcome
- ToT, primary outcome
- PFS, secondary outcome
- OS, exploratory outcome.

The remaining outcomes, which do not inform the economic model, are based on data from the November 2018 data cut:

- ORR, primary outcome
- DoR, secondary outcome
- DCR, part of ORR
- CBR, secondary outcome
- Time to treatment, exploratory outcome

The CS does not report an HRQOL outcome. HRQoL is an outcome in the NICE scope and CS Table 1 indicates that it would be addressed in the CS. However, CS section B.3.4.1 states that no HRQoL data were collected in the NAVIGATOR study. Data for HRQoL in the company's economic model are sourced from the published literature.

ERG conclusion

All included outcomes are clinically relevant and match the scope and decision problem, except for HRQoL which was not assessed in the pivotal NAVIGATOR study. Whilst the outcomes used in the economic model are appropriate and all use the latest data cut, the survival data remain immature.

3.2.4 Approach to study statistics

The statistical approaches for each outcome, except for ToT, are defined in CS Table 8.

The statistical analysis plan (SAP) for NAVIGATOR was provided in response to clarification question A1. In addition to the information in CS Table 8 the SAP states that descriptive statistics will be provided for ToT.

Data are immature. Median OS and DoR have not been reached, and so results for OS, PFS and ORR should be treated with caution. CS section B.2.11 reports that follow up is ongoing for survival. No details of any further potential data cuts are provided.

The ERG believe that the appropriate statistical methods have been applied for analysing each outcome. OS, PFS, and DoR were analysed using Kaplan-Meier methods, with variance tested using Greenwood's formula, a common Kaplan-Meier estimator.[35] ORR and CBR were estimated using frequency, percentage and 95% confidence intervals based on the exact binomial distribution.

The NAVIGATOR CSR[17] states that no formal adjustments for possible covariate effects were planned. However, CS Table 8 describes adjustments for ORR (the CS presents a list of covariates used to fit a logistic regression), PFS (used estimated hazard ratios of confounding factors), and OS (stratified Cox regression analysis using mutation type as a stratification factor; CSR page 84).

3.2.4.1 Sample size and power calculation

CS Table 8 reports that a sample size of 31 patients would be required for 90% power to test the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 35% using an exact binomial test, and assuming a two-sided Type 1 error rate of 0.05. As the sample of patients with the *PDGFRA* D842V mutation in the study 56, the ERG is satisfied that the study is adequately powered for this particular hypothesis test.

3.2.4.2 Analysis populations

The clinical effectiveness analysis population of NAVIGATOR is defined as patients with the *PDGFRA* D842V mutation (N=56). This is a pre-specified subgroup (Group 2) of the safety population of the NAVIGATOR study (N=237).

The safety analysis population of NAVIGATOR includes all patients in the study with unresectable or metastatic GIST with any mutation, not limited to *PDGFRA* D842V (N=237).

The NAVIGATOR SAP states that all primary analyses will be conducted and presented by starting daily dose (grouped as <300mg, 300mg, 400mg, 300/400mg and 'all doses'). The 'all doses' group is the company's preferred analysis population, as reported for the clinical effectiveness results in CS section B.2.6. The ERG and our clinical experts agree that dose pooling is appropriate (see section 3.2.1).

3.2.4.3 Subgroup analyses

According to the NAVIGATOR SAP, comparisons of the different avapritinib dose groups were pre-specified, albeit descriptively without formal statistical testing being mentioned. CS Appendix L presents descriptive comparisons between the 300mg QD, 400mg QD and all-doses groups for overall survival (CS Appendix Table 51; CS Appendix Figure 12), progression-free survival (CS Appendix Table 52; CS Appendix Figure 13), overall response rate (CS Appendix Table 53), duration of response (CS Appendix Table 54), and time to response (CS Appendix Table 55). Results for the <300mg group are not reported in the CS but can be found in the CSR.[17]

Comparisons of adverse event frequencies were also made between these dose groups (CS Appendix F), as discussed in section 3.2.6 below.

3.2.4.4 Missing data

The CS does not explicitly discuss missing data in the NAVIGATOR study. The CSR states that, in general, no imputation was performed for missing data points (CSR section 11.3.2). However, the CS reports sample sizes alongside the clinical effectiveness outcomes which suggest that for most outcomes all available study participants were included in analyses.

Sensitivity analyses were carried out for DoR and PFS (CS Table 8). For DoR, FDA[37] censoring rules were used in the primary analysis and a sensitivity analysis was carried out using EMA[38] censoring rules. Detailed FDA[37] and EMA[38] censoring rules for PFS and DoR are reported in Table 4 of the NAVIGATOR SAP. The company clarified at the factual error check stage that PFS censoring followed EMA rules. The CS states that if a patient had not had an event, PFS was censored at the date of last valid assessment that was stable or better (CS Table 8). The CS reports DoR using the results of the sensitivity analysis (the EMA rules); however, only one less patient was censored by these rules and the Kaplan-Meier estimates remained the same (CSR Tables 14.2.2.1.2 and 14.2.2.2.2).

ERG conclusion

The ERG are satisfied that the company's approach to statistics is generally appropriate: the study was adequately powered and the latest available data were used to inform the survival statistics.

3.2.5 Clinical effectiveness results

Clinical effectiveness results are reported for NAVIGATOR in CS section B.2.6 and CS Appendix L; for BLU-285-1002 in CS Tables 9 and 11, CS Appendix Tables 14, 16 and 17, and CS Appendix N.4; and for the Cassier study in CS Tables 15 to 17 and CS Appendix P.

Below we present a summary of results from NAVIGATOR for the primary outcome of ORR, related response outcomes (including DCR, CBR and DoR) and time-to-event outcomes used in the economic model (OS, PFS, time to response, time on treatment), alongside those from the BLU-285-1002 and Cassier studies where available. We note that:

- Radiographic tumour reductions are reported in the CS but are not in the decision problem nor used in the economic model and are therefore not commented upon here.

- Results appear consistent for each outcome across the dose subgroups, although the sample sizes are relatively small (CS Appendix L).
- Data for time-to-event outcomes (OS, PFS, DoR) are immature and therefore have increased uncertainty relative to a mature data set.

3.2.5.1 Overall Response rate (ORR)

The ORR and related response outcomes are shown in Table 6. No patients in the ECM studies achieved a response, compared to [redacted] % in the avapritinib study.

Table 6 Overall response rate in the avapritinib and ECM studies

	Avapritinib	ECM		
	NAVIGATOR All doses group (N=56)	BLU-285-1002 Unresectable/ metastatic group (N=19)		Cassier et al 2012 *PDGFRA* subgroup (N=32)
ORR outcome		2nd line n=19	3rd line n=16	
ORR, n (%) [95% CI]	[redacted] 300mg dose [redacted]	[redacted]	[redacted]	0 (0)
Complete response	[redacted]	[redacted]	[redacted]	0 (0)
Partial response	[redacted]	[redacted]	[redacted]	0 (0)
Stable disease	[redacted]	[redacted]	[redacted]	10 (31)
Progressive disease	[redacted]	[redacted]	[redacted]	21 (66)
Other	[redacted]	[redacted]	[redacted]	1 (3) [a]
CBR, n (%) [95% CI]	[redacted]	Not reported		Not reported
DCR, n (%) [95% CI]	[redacted]	Not reported		Not reported

Source: NAVIGATOR: CS section B.2.6.3; BLU-285-1002: CSR; Cassier: study publication.
CBR: clinical benefit rate; DCR: disease control rate (see Appendix 4 for definitions)
[a] Includes not evaluable and not assessed (in Cassier study 1 patient died before first assessment)

3.2.5.2 Duration of Response (DoR)

The available data for duration of response in NAVIGATOR are shown in Table 7.

Table 7 Duration of response in the NAVIGATOR study

DoR, Kaplan-Meier estimates	
Median (months) (95% CI)	All doses: [redacted]
	300mg dose [redacted]
3 months, % (95% CI)	[redacted]
6 months, % (95% CI)	[redacted]
9 months, % (95% CI)	[redacted]
12 months, % (95% CI)	[redacted]
18 months, % (95% CI)	[redacted]
24 months, % (95% CI)	[redacted]
Source: CS section B.2.6.4	

3.2.5.3 Overall Survival (OS)

Median estimates of overall survival in NAVIGATOR are shown in Table 8 (from CS Table 9). The NAVIGATOR OS Kaplan-Meier curve is provided in CS Figure 3 (not reproduced here). At 42 months [redacted]% of patients were still alive, and that had not changed from the 30-month time point. Median OS is [redacted] at the latest (January 2020) data cut. In contrast, median OS was [redacted] months and [redacted] months for second- and third-line therapy respectively in BLU-285-1002, and 14.7 months in the Cassier study.

Table 8 Overall survival in the avapritinib and ECM studies

	Avapritinib	**ECM**	
OS, Kaplan-MOSeier estimates	**NAVIGATOR All doses group (N=56)**	**BLU-285-1002 Unresectable/ metastatic group (N=19)**	**Cassier et al 2012 *PDGFRA* subgroup (N=32)**
Median follow-up, months	[redacted]	Not reported	45.3 [a]
Median OS, months (95% CI)	[redacted]	[redacted]	14.7 (not reported)
6 months, %	[redacted]	Not reported	Not reported
12 months, %	[redacted]	Not reported	Not reported
18 months, %	[redacted]	Not reported	Not reported
24 months, %	[redacted]	Not reported	Not reported
30 months, %	[redacted]	Not reported	Not reported
36 months, %	[redacted]	Not reported	Not reported
42 months, %	[redacted]	Not reported	Not reported

Source: NAVIGATOR: CS section 2.6.1; BLU-285-1002: CS Appendix Table 17; Cassier: study publication.
[a] median follow-up for surviving patients

Although no subgroup analyses were planned for UK NAVIGATOR patients within the *PDGFRA* D842V mutation subgroup, the CS notes that [redacted] of the [redacted]) UK patients in the study were still alive at the time of the January 2020 data cut, with a median follow-up of [redacted] months. This is relevant to the appraisal and the results are in line with the rest of the study population.

3.2.5.4 Progression Free Survival (PFS)

Median estimates of progression-free survival are shown in Table 9 (from CS Table 10). The NAVIGATOR PFS Kaplan-Meier curve is provided in CS Figure 4 (not reproduced here). Median PFS was [redacted] at the latest (January 2020) data cut compared with only [redacted] to [redacted]months in the ECM studies. In NAVIGATOR [redacted]% of patients were alive and progression free at 42 months. We note that the reported duration of PFS was longer for patients receiving third- line than for those receiving second-line therapy in BLU-285-1002, although these estimates are uncertain (sample sizes are small and confidence intervals wide).

Table 9 Progression-free survival in the avapritinib and ECM studies

	Avapritinib	**ECM**	
PFS, Kaplan-Meier estimates	**NAVIGATOR All doses group (N=56)**	**BLU-285-1002 Unresectable/ metastatic group (N=19)**	**Cassier et al 2012 *PDGFRA* subgroup (N=32)**
Median, months (95% CI)	[redacted]	[redacted]	2.8 (2.4 to 3.2)
6 months, %	[redacted]	Not reported	8 patients (25%) had PFS longer than 6 months (range 6.4 to 50.8 months)
12 months, %	[redacted]	Not reported	
18 months, %	[redacted]	Not reported	
24 months, %	[redacted]	Not reported	
30 months, %	[redacted]	Not reported	
36 months, %	[redacted]	Not reported	
42 months, %	[redacted]	Not reported	
Source: NAVIGATOR: CS section B.2.6.2; BLU-285-1002: CS Appendix Table 17; Cassier: study publication.			

3.2.5.5 Time to Response

The median time to response was [redacted] days in the all-doses group of the NAVIGATOR study. Time to response was not reported for the ECM comparator studies.

3.2.5.6 Time on treatment (ToT)

Median estimates of time on treatment are shown in Table 10 for the NAVIGATOR study, for both the *PDGFRA* D842V population and the safety population. Time on treatment was not reported in the BLU-285-1002 and Cassier studies.

Table 10 Time on treatment in the NAVIGATOR study

ToT, Kaplan-Meier estimates	Analysis population		
	***PDGFRA* D842V group (N=56) January 2020 data cut**	***PDGFRA* D842V group (N=56) November 2018 data cut**	**Safety population (N=237) November 2018 data cut**
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
6 months, %	[redacted]	Not reported	Not reported
12 months, %	[redacted]	Not reported	Not reported
18 months, %	[redacted]	Not reported	Not reported
24 months, %	[redacted]	Not reported	Not reported
30 months, %	[redacted]	Not reported	Not reported
36 months, %	[redacted]	Not reported	Not reported
42 months, %	[redacted]	Not reported	Not reported

Source: CS Tables 21 to 23.
[a] reported in the CS in weeks, converted to months by ERG

3.2.5.7 HRQoL outcomes

CS section B.3.4.1 states that no HRQoL data were collected in the NAVIGATOR study, and CS section B.2.13.2 discusses the lack of HRQoL data for the specific *PDGFRA* D842V mutation population of patients with unresectable of metastatic GIST as a limitation of the evidence base overall. Sources of HRQoL data for the company's economic analysis were taken from the published literature (see section 4.2.7 below).

3.3 Safety outcomes

The company's economic model includes Grade 3-4 adverse events with incidence of greater than 2% in either arm. The avapritinib arm also includes any comparator adverse events with greater than 2% incidence (CS section B.3.3.5) (see section 4.2.7.4 below).

3.3.1 Current submission

Adverse events are reported in CS section B.2.10 for the entire safety population of the NAVIGATOR study (N=237), not limited by the type of mutation or starting dose of avapritinib (therefore including patients without the *PDGFRA* D842V mutation, treated at fourth line, following failure of imatinib, sunitinib and regorafenib). The company argue, and the ERG's clinical experts agreed, that the full NAVIGATOR population provides the maximum amount of data available on the safety of avapritinib and is appropriate as a reference since there is no evidence to suggest that presence or absence of the *PDGFRA* D842V mutation would affect the frequency of adverse events.

The company report adverse events separately for the 300mg and 400mg QD dose subgroups of the entire NAVIGATOR study population (N= and N= respectively) and the combined 300mg+400mg group (N=) in CS Appendix F. Frequencies of adverse events are similar when the combined 300mg+400mg QD subgroup (N=) is compared against the all-doses group (N=237) (CS Appendix Table 23).

Overall, % of all patients in NAVIGATOR who received avapritinib (N=237) had experienced at least one adverse event at the November 2018 data cut (median duration of treatment weeks). The most frequent adverse events were nausea (%), fatigue (%), and anaemia (%), with a wide range of other adverse events occurring at lower frequencies (CS Table 25). Adverse events of Grade 3 or above occurred in % of patients, whilst serious adverse events occurred in %. Adverse events leading to avapritinib discontinuation, dose interruption or dose reduction occurred, respectively, in %; % and % of patients. Overall, % of patients died within 30 days of receiving their last dose of avapritinib (CS Appendix Table 22), mostly as a result of progressive disease.

The overall high frequency of any adverse events is consistent with those in the comparator TKIs (imatinib 98%, sunitinib 94%, regorafenib 100%) (CS Table 29). However, the frequency of adverse events of Grade 3 or more was higher in the NAVIGATOR all-doses

population ([redacted]%) than among patients receiving imatinib (52.4%). A caveat is that it is difficult to directly compare rates of different types of adverse events across the TKIs due to differences in how the events were defined and reported.

The company identified cognitive effects and intracranial bleeding as adverse events of special interest among patients receiving avapritinib. Cognitive effects were experienced by [redacted]% of patients overall, with the most frequent being memory impairment ([redacted]%), cognitive disorder ([redacted]%), confusional state ([redacted]%) and encephalopathy ([redacted]%). Intracranial bleeding occurred in three patients ([redacted]%) (CS Table 27).

The majority of cognitive adverse events were Grade 1 or Grade 2. The only cognitive adverse event of Grade 3 or more reported with an incidence of ≥2% (as measured in the 300mg/400mg dose group) was confusional state ([redacted]%).

The company conducted a post-hoc descriptive analysis of cognitive effects to clarify the safety and tolerability of the 300mg QD avapritinib dose in relation to these adverse events (CS section B.2.10.7.1). This included the population of patients who received the 300mg QD dose of avapritinib in the NAVIGATOR study and the ongoing VOYAGER trial (total N=184) (VOYAGER is described in section 3.2.1 above). The analysis demonstrated similar frequencies of cognitive effects to those seen in the all-dose group in NAVIGATOR (CS Table 28). Cognitive effects led to dose interruption in [redacted]% of patients and dose reduction in [redacted]%. The post-hoc safety analyses reports that Grade 3 or above adverse events for cognitive impairment were: confusional state (1%), cognitive disorder (<1%), encephalopathy (<1%), and memory impairment (0%). No patients in the post-hoc safety analysis experienced adverse events for any cognitive effects of Grade 4 or above.

3.3.2 FDA safety assessment

The US Food and Drug Administration (FDA) have conducted a detailed assessment of the safety of avapritinib based on data submitted by the company.[30] The primary safety population in the FDA assessment was defined as all patients in NAVIGATOR who received avapritinib doses of 300mg or 400mg QD (N=[redacted]). Additional safety data were examined from the phase 3 VOYAGER trial of patients with advanced GIST (BLU-285-1303) and a dose-finding study of avapritinib use in patients with advanced systemic mastocytosis (EXPLORER; BLU-285-2101). As would be expected, the FDA and ERG reached similar conclusions on the safety of avapritinib. The key conclusions from the FDA assessment[30] were:

- The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with avapritinib, and the duration of treatment is adequate to allow assessment of adverse reactions over time.
- The proposed 300mg QD dosage has a manageable safety profile.
- The 300mg QD dose appears to be better tolerated than 400mg QD; specifically, a higher incidence of Grade 3+ adverse events (82% versus 67%), adverse events leading to dose reduction (66% versus 41%) and cognitive adverse events of special interest (48% versus 35%) occurred in the 400mg QD starting dose group compared to 300mg QD.
- The frequency of some treatment-emergent adverse events varied with age; however, due to the single-arm study design it is not possible to conclusively say whether the differences were due to age alone.
- The frequency of some treatment-emergent adverse events varied with race; however, due to dominance of the data by people with white race, it is unclear whether adverse event frequencies do differ consistently between racial groups.
- Intracranial bleeding is a rare but significant adverse event likely related to avapritinib.
- Central nervous system (CNS) effects occurred in [redacted]% of patients, of which [redacted]% were Grade 3 or Grade 4. Avapritinib was permanently discontinued due to CNS effects in [redacted]% of patients. Cognitive impairment was more frequent in patients aged over 65 years.
- The pharmacokinetics of avapritinib in people with severe hepatic impairment requires investigation.

ERG conclusion

Avapritinib has a manageable safety profile which has some broad similarities with the safety profiles of the comparator TKIs, although comparisons are difficult due to differences in how adverse events are defined and recorded. Avapritinib is uniquely associated with cognitive effects which, in clinical studies, required dose interruption and/or reduction in [redacted]% of patients.

3.4 Critique of studies included in the indirect treatment comparison

3.4.1 Rationale for the ITC

The comparison of interest is avapritinib versus established clinical management (ECM), where ECM reflects the use of TKI therapy and/or best supportive care.

As noted above in section 3.2.1, a single-arm study on avapritinib and two single-arm studies on various ECM comparators were available, but no studies have directly compared avapritinib against ECM. An indirect treatment comparison was therefore necessary.

3.4.2 Identification, selection and feasibility assessment of studies for the ITC

As noted in section 3.2.1 above, the company identified seven studies that provide data on patients with the *PDGFRA* D428V mutation who received avapritinib or ECM. Four of these studies had very small sample sizes (N=3 to N=12) and were not considered in detail by the company. The remaining three studies on avapritinib (NAVIGATOR, N=56) and on ECM (BLU-285-1002, N=22 and the Cassier study, N=32) were selected for inclusion in indirect comparisons. The ERG agree with the company that these studies are the most appropriate for the ITC.

3.4.3 Clinical heterogeneity assessment

Table 4 and Table 5 in section 3.2.1 above compare the study and patient characteristics, respectively, across the three studies. Heterogeneity among the studies is evident as follows:

- There are differences between NAVIGATOR and BLU-285-1002 in terms of age, race, geographical region, tumour size, and prior therapies.
- Prior TKI therapy received is not reported in the ECM studies for the relevant *PDGFRA* D842V mutation subgroup (Table 5 above).
- ECOG performance status was recorded as missing for all but one of the BLU-285-1002 patients.
- Patient-level baseline characteristics in the Cassier study were unavailable for the *PDGFRA* D842V mutation subgroup (32/58=55%), precluding a qualitative assessment of heterogeneity.

An important aspect of heterogeneity assessment is to establish whether the studies differ on key prognostic factors. This is discussed in section 3.5.2 below.

3.4.4 Similarity of treatment effects

- The company's ITC approach covers OS and PFS outcomes which appear comparable across the studies.
- The proportions of patients receiving each line of treatment differed between the ECM comparator studies (CS Appendix Figures 30 and 31).

- The Cassier study second-line cohort appears to fare notably worse on PFS than the BLU-285-1002 third-line cohort (CS Appendix Figures 30 & 31). As such, the base case adjusted ITC (NAVIGATOR versus BLU-285-1002) could be viewed as more conservative than the unadjusted scenario ITC (NAVIGATOR versus the Cassier study).

3.4.5 Risk of bias assessment for RCTs included in the ITC

- As noted above in section 3.2.2, the included studies are inherently at risk of selection bias due to their single-arm designs and, in the case of the comparator studies, also their retrospective methods.
- The bias risk arising from the lack of a comparator group in each study may be reduced if studies can be well-matched on all key prognostic factors and effect modifiers in an ITC (although "perfect" matching is considered very difficult if not impossible to achieve).
- The inherent bias risk arising from the comparator studies being retrospective (i.e. possibility of selective "cherry picking" of cases or results) cannot be reduced using ITC methods.
- As summarised in Table 11, both the adjusted and unadjusted indirect comparisons are at risk of bias, with the unadjusted comparison with the Cassier study being particularly at high risk of bias due to the lack of any matching of covariates. These comparisons are illustrative, since the risk of bias cannot be quantified.

Table 11 Overview of bias risk for studies included in the ITC

Bias source	NAVIGATOR versus BLU-285-1002	NAVIGATOR versus Cassier
Inherent risk of bias due to single-arm design [a]	Yes in both studies but possibly reduced by matching in ITC	Yes in both studies but cannot be reduced (no matching)
Inherent risk of bias due to retrospective methods [b]	Yes in BLU-285-1002 – cannot be reduced by ITC methods	Yes in Cassier study – cannot be reduced by ITC methods
[a] this covers several domains of bias e.g. selection bias, performance bias and confounding which single-arm studies are prone to [b] bias due to selective ascertainment of cases and/or results		

ERG conclusion

The company employed ITC as the method of data synthesis, which is appropriate given the lack of any comparative studies. One avapritinib study and two ECM

studies are eligible for comparison. All three studies have inherent risks of bias arising from their single-arm designs and, in the case of the two ECM studies, also due to their retrospective ascertainment of patient records. The studies exhibit heterogeneity in several baseline characteristics. Some baseline characteristics of the ECM studies, including prior TKI use, are not fully clear due to not being reported specifically for the PDGFRA D842V mutation subgroup of patients with unresectable or metastatic GIST.

3.5 Critique of the ITC methods

3.5.1 Overview of the company's ITC approach

The CS reports that the following ITCs were conducted:

- An adjusted ITC using propensity score weighting was conducted to compare NAVIGATOR and BLU-285-1002. This is an appropriate methodology for this comparison since the company had access to individual patient-level data (IPD) for both studies.
- An unadjusted (naïve) ITC was conducted to compare NAVIGATOR and the Cassier study (CS Appendix Tables 14 to 17). The CS states that an adjusted comparison was not feasible since the Cassier study publication reported inadequate information on baseline characteristics of the patients in the *PDGFRA* D842V subgroup to enable statistical matching of the studies (as noted above in Table 5, some baseline characteristics are missing and those that are reported are for the whole study group, not specifically for the *PDGFRA* D842V subgroup).

The company favoured the adjusted comparison as their primary comparison and the unadjusted comparison as a sensitivity analysis. We agree that the company's approach is appropriate, given the heterogeneity among studies noted above in section **Error! Reference source not found.**, since an adjusted ITC is preferable for reducing imbalances in prognostic factors and effect modifiers and, hence, for minimising the risk of bias arising from the comparison.

We also agree with the company that an adjusted comparison of the NAVIGATOR and Cassier studies would not be feasible and therefore only a naïve comparison could be made. A possible advantage of including the Cassier study in a naïve comparison would be that the cohort was Europe-based whilst the BLU-285-1002 study consisted solely of US patients, and therefore the company's combination of adjusted and naïve ITCs in their primary comparison and sensitivity analyses respectively would make best use of the available

comparator data. However, the following limitations of the naïve comparison should be kept in mind:

- Relatively few patient characteristics can be compared between NAVIGATOR and the Cassier study (Table 5);
- Some of those characteristics that can be compared are heterogeneous across the studies (Table 5);
- The Cassier study does not report any baseline characteristics for the *PDGFRA* D842V subgroup (Table 5). Clinical experts advising the ERG suggested that patient characteristics would be unlikely to differ between the overall unresectable/metastatic population and those with the PDGFRA D842V mutation in the Cassier study. However, the ERG is uncertain whether prior TKI use would have been homogeneous, given that TKI clinical effectiveness differs between these population groups.
- The Cassier study (as with BLU-285-1002) is at risk of selection bias due retrospective data collection.

3.5.2 Data inputs to the adjusted ITC

In CS Appendix D, page 26, the company note that "some factors potentially associated with treatment outcomes were identified". The ERG, concerned that the list of prognostic factors may be incomplete, requested clarification of the evidence in support of prognostic factors (clarification questions A2 and A3). The company responded that no established evidence for prognostic factors exists given the small numbers of patients with the *PDGFRA* D842V mutation, although they suspect that ECOG performance status could be related to outcomes as is often the case in oncological indications. The company reported they thus used a comprehensive approach that included all available potentially relevant prognostic factors in the ITC (CS Appendix D Table 8). The ERG's experts agreed the list to be comprehensive.

However, the propensity score weighting did not include tumour size nor the specific previous TKIs. No explanation is given in the CS for why these covariates have not been included in the adjusted ITC analysis. The company clarified (at the factual inaccuracy check stage) that tumour size was only measured at the time of diagnosis, not at the time of initial treatment for unresectable or metastatic disease; and that inclusion of the specific prior TKIs received was not feasible due to the small sample size. It is unclear whether these covariates could be prognostic or what the effect of including/excluding them from the propensity score weighting exercise would be. Nevertheless, despite this weakness, the

ERG agree that adjusting for some of the prognostic factors is preferable to a naïve indirect comparison adjusting for none.

The continuous variables age and disease duration were dichotomised in the propensity score weighting (see Table 5). It was unclear to the ERG why this was done (clarification question A4). In response, the company conducted a series of sensitivity analysis using different cut-offs and continuous variables; none of these analyses improved model fit.

The company excluded race and ECOG performance status from the propensity score weighting analysis due to missing values. In response to clarification question A7, the company conducted a sensitivity analysis including race in the analysis which had little impact on OS or PFS. Furthermore, the ERG's experts were unaware of any prognostic effect of race.

3.5.3 Statistical methods for the adjusted ITC

For the adjusted ITC the company used an inverse probability weighting (IPW) method. Using IPW, outcomes are weighted by the inverse of the propensity score which is the probability of a patient with a given covariate set being assigned to a treatment. Avapritinib (i.e. the NAVIGATOR cohort) was selected as the reference treatment so patients' propensity score weights were estimated as the probability that a patient belongs to the ECM cohort (i.e. BLU-285-1002). Thus, ECM patients with a higher propensity score, and hence a lower IPW, had a lower probability of belonging to the NAVIGATOR cohort, and vice versa. The IPW method was preferred by the company over an alternative possible method, propensity score matching, as setting a matching threshold (caliper) could have led to the exclusion some patients in an already small dataset (clarification response A10). A logit regression including all prognostic factors was used to estimate the propensity score.

The company presented Kaplan Meier curves and median OS and PFS estimates for each indirect treatment comparison but did not report relative treatment effects in terms of hazard ratios (HR) (presumably because these were not required for the economic model). The ERG requested the company to report HRs for the comparisons of NAVIGATOR against BLU-285-1002 (IPW adjusted ITC) and NAVIGATOR against the Cassier study (unadjusted ITC) in clarification question A6. These results are provided in section 3.5.5 below.

CS Appendix N.3 shows that two patients from BLU-285-1002 had relatively high inverse propensity score weights (and therefore low propensity scores), and therefore may have had

a disproportionate impact on the analysis. The ERG asked the company to repeat the analysis removing these two patients in clarification question A9. The company ran this analysis but qualified this by stating that they did not consider this a valid analysis. The ERG agrees since this removes the two patients most resembling NAVIGATOR from BLU-285-1002. Nevertheless, it does show the analysis is sensitive to the inclusion of these two patients and illustrates uncertainty due to the small sample size (i.e. the analysis would be less sensitive to the inclusion of these two patients if the sample size was larger).

The ERG also queried whether the IPW exercise had been wholly successful (clarification question A10), since differences in the mean values of certain patient characteristics between NAVIGATOR and BLU-285-1002 were greater post-IPW than pre-IPW (CS Appendix N.2, Table 58). The largest differences in pre-IPW means were for age, ethnicity, and total number of TKIs. Although there is still some misalignment of these characteristics (including total number of TKIs) post-IPW, the company argued that the overall effect is of an improvement in terms of balanced patient characteristics post-IPW. Further scenario analyses around the inclusion of covariates provided in clarification response A10 support the company's conclusion. Based on this, the ERG accept the company's argument.

NICE DSU Technical Support Document 17 recommends that sensitivity analyses are conducted using different matching methods and using different covariate sets and functional form for continuous covariates (e.g. polynomials, interactions) to test the stability of the results. No such analyses are presented in the CS, hence this was queried by the ERG in clarification question A11. The company subsequently presented a series of scenario analyses using a backwards stepwise selection process and a probit model to calculate the propensity score. Backward selection is an automated regression process which starts with the model including all covariates then sequentially removes the least predictive covariate until all remaining covariates are statistically significant. (The level of statistical significance used by the company is not reported.) The most parsimonious stepwise model included age and number of TKIs (clarification response Table 7). The ERG acknowledge that visually there is little difference in the Kaplan Meier curves between the parsimonious model and full covariable model for OS or PFS and between the logit and probit models (clarification response Figures 8 and 9).

There is some variation in the unadjusted and IPW-adjusted Kaplan Meier curves, resulting in a downward shift of the OS curve for ECM (clarification response Figure 8). PFS was similar in the adjusted and unadjusted analyses (clarification response Figure 9).

It should be noted that the outputs of the ITC are not used directly in the economic model. The OS and PFS inputs to the economic model are taken from the extrapolation of the IPW Kaplan Meier curves.

The analysis was conducted in Stata 13. In response to clarification question A5, the company provided the data and Stata code. The ERG checked the code and confirmed that the models had been correctly applied.

The ERG were able to replicate the CS results for OS and PFS in terms of Kaplan Meier curves and survival at key time points, but we were unable to replicate the hazard ratio for PFS reported in clarification response A3. Fitting a Cox proportional hazards model to the IPW-adjusted Kaplan Meier OS model resulted in a HR of 4.42 (95% CI 2.09, 9.34) which approximates the company's results but the PFS HR of 11.81 (95% CI 4.79, 29.15) is less favourable to ECM than the company's analysis. The reason for the discrepancy is unclear but, in any case, the HRs are not used in the economic model.

3.5.4 Results from the adjusted ITC

3.5.4.1 Overall survival

- The IPW-adjusted Kaplan Meier curves and median survival estimates for NAVIGATOR and BLU-285-1002 are reproduced in Figure 2 and Table 12 below.
- The OS hazard ratio for ECM versus avapritinib (clarification response A6) is [redacted]

[redacted]

Source: Reproduction of CS Figure 6

Figure 2 IPW-adjusted Kaplan–Meier curves for OS in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Table 12 IPW-adjusted Kaplan–Meier survival estimates of OS at key timepoints in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Kaplan–Meier survival estimates	NAVIGATOR	BLU-285-1002
Median, months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Source: Reproduced from CS Table 17		

3.5.4.2 Progression-free survival

- The IPW-adjusted Kaplan Meier curves and median PFS estimates for NAVIGATOR and BLU-285-1002 are reproduced in Figure 3 and Table 13 below.
- The PFS hazard ratio for ECM versus avapritinib (clarification response A6) is [redacted]

[redacted]

Source: Reproduction of CS Figure 7

Figure 3 IPW-adjusted Kaplan–Meier curves for PFS in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Table 13 IPW-adjusted Kaplan–Meier survival estimates of PFS at key timepoints in the NAVIGATOR study (avapritinib) and BLU-285-1002 (ECM)

Kaplan–Meier PFS estimates	NAVIGATOR	BLU-285-1002
Median, months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Source: Reproduction of CS Table 19		

3.5.5 Comparison of results from the adjusted and unadjusted ITCs

- Kaplan Meier curves, their extrapolation, and survival estimates over time for the Cassier study are presented in CS Appendix P. Hazard ratios for OS and PFS were provided by the company at the ERG's request. These are reproduced in Table 14 below, alongside those from the adjusted ITC analysis.
- The HRs from the adjusted and naïve analyses are in broad agreement. However, we caution that both analyses are subject to uncertainty, particularly the unadjusted comparison (see section 3.5.1 above). The results are based on relatively small sample sizes, meaning that confidence intervals for the HRs are relatively wide. Furthermore, the ITC results are at risk of bias, as summarised in Table 11 above, which adds further uncertainty that is not captured within the confidence intervals.

Table 14 Hazard ratios for median OS and PFS from the adjusted and naïve indirect comparisons

Outcome	Hazard ratio, ECM versus avapritinib (95% CI)	
	BLU-285-1002 versus NAVIGATOR, adjusted ITC	**Cassier study versus NAVIGATOR, unadjusted (naïve) ITC [a]**
Overall survival	[redacted]	[redacted]
Progression-free survival	[redacted]	[redacted]

Source: Clarification response A6
[a] The ERG assume these results are for the Cassier study PDGFRA D842V subgroup rather than for the whole unresectable/metastatic GIST population but this is not stated in the clarification response

3.5.6 Summary of the ERG's critique of the indirect comparisons

- The methodology followed by the company is appropriate given the data limitations
- The methodology has been described and applied correctly
- A thorough set of sensitivity analyses was conducted by the company
- However, three potentially relevant covariates (performance status score, specific prior TKIs received, and tumour size) could not be included in the model due to limitations of the data. The effect of this is unclear.
- The IPW analysis has been effective but remains uncertain given the choice of prognostic factors and small size of the PGDFRA D842V mutation population
- The outputs of the ITC are not used directly in the economic model. The OS and PFS inputs to the economic model are taken from the extrapolation of the IPW Kaplan Meier curves.

3.6 Conclusions of the clinical effectiveness section

The ERG's critique of the company's synthesis of clinical effectiveness evidence has identified a number of issues, as summarised in Table 15. As indicated in the table, some of these issues cannot easily be resolved unless further clinical effectiveness evidence becomes available, whilst other issues have been resolved or partly resolved.

Table 15 Key clinical effectiveness issues identified by the ERG

Issue	Where discussed	ERG comments
The clinical pathway is unclear and differs between the submitted evidence and expected UK clinical practice	Sections 2.2.3.1 and 3.2.1.3	Unclear whether resolvable by wider clinical consultation to reduce uncertainty around UK clinical practice or company clarification on the rationale for TKI use in the clinical studies. Prior TKI use in PDGFRA D842V patients would be expected to be lower than that seen in the company's studies given that TKIs lack clinical effectiveness in this group.
OS, PFS and DoR outcomes are immature	Sections 3.2.4 and 3.2.5Clinical effectiveness results	Not resolvable until the pivotal NAVIGATOR study is completed (or a more recent data cut provided)
Clinical evidence is based on small sample sizes	Section 3.2.1	Not resolvable without collecting further data – difficult in this small population subgroup
ECM comparator studies were retrospective and hence at risk of selection bias	Sections 3.2.2 and 3.4.5	Not resolvable without conducting further, prospective, protocol-based, studies (or retrospective studies with random sampling and blinding) – difficult in this small population subgroup
There is a lack of head to head comparative evidence.	Sections 3.2.1 and 3.4.1	This is partly resolvable by ITC, albeit with key uncertainties
Unclear whether all prognostic factors were accounted for in adjusted ITC (NAVIGATOR versus BLU-285-1002)	Section 3.5.2	Performance status score, tumour size and specific prior TKIs received could not be included as covariates in the analysis due to data limitations. It is unclear whether these would be influential as prognostic factors. Not resolvable without collecting further data – difficult in this small population subgroup
Adjusted ITC not feasible for NAVIGATOR versus Cassier	Section 3.5.1	The naïve ITC should be considered weaker than the adjusted ITC (increased risk of bias from lack of matching) so should be interpreted with caution. This issue might be resolvable if further data or

comparison and naïve ITC highly uncertain		clarification could be obtained from the Cassier study authors. However, although data from the Cassier study inform an economic scenario analysis, these are taken directly from the study rather than from the ITC (section 4.2.6 below)
Lack of HRQoL data for avapritinib	Section 3.2.5.7	Prospective data collection would be preferred. Resolved for now by using literature based HRQoL estimates for the economic model (section 4.2.7) and some HRQoL data from VOYAGER study in an ERG scenario (section 6.2)

4 COST EFFECTIVENESS

4.1 ERG comment on the company's review of cost-effectiveness evidence

The company conducted a systematic literature review of cost-effectiveness studies published from January 2009 until December 2019 for patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST (CS section B.3.1 and CS Appendix G).

The following electronic databases were searched: MEDLINE® In-Process, Embase® and MEDLINE, EconLit®, Centre for Reviews and Dissemination York for Health Technology Assessment Database and National Health Service Economic Evaluation Database. In addition, the company searched conferences to identify relevant abstracts and key international HTA databases to identify relevant HTA evaluations.

The company applied inclusion and exclusion criteria to select relevant economic evaluation studies, which are listed in CS Appendix Table 30. The company's review did not identify any relevant cost-effectiveness studies assessing patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST. Therefore, studies for the general unresectable or metastatic GIST population were considered for inclusion, based on the assumption that quality of life and resource use are similar among patients, regardless of their mutational status. Twenty-one publications for the general GIST population were identified (CS Appendix Figure 5 and CS Table 31). Of these studies, three were previous NICE Technology Appraisals for avapritinib comparators: TA86/TA209 for imatinib,[11,39] TA179 for sunitinib[12] and TA488 for regorafenib.[13] The remaining 18 studies were from international healthcare settings and/or reported the same data used in previous NICE appraisals. The main characteristics of the three previous NICE appraisals are summarised in CS Table 31.

The ERG updated the company's search and one additional study met the inclusion criteria.[40] This study assessed the clinical effectiveness, safety and cost-effectiveness of different sunitinib doses in unresectable or metastatic GIST and different axitinib doses in metastatic renal cell carcinoma. The resource use and cost expenditures were obtained from a Dutch perspective and the authors did not report health state utility values.

ERG conclusion

The ERG consider the company's review of cost-effectiveness evidence adequate and comprehensive, albeit a few months out of date. The company's review did not identify any relevant cost-effectiveness studies assessing patients with unresectable or

metastatic *PDGFRA* D842V-mutated GIST. The additional study found by the ERG[40] does not present any further relevant information for the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 16 shows that the company's economic evaluation adheres to the NICE reference case requirements.

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes, discussed in CS Appendix D and Appendix H
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, EQ-5D data collected from previous NICE appraisals
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, utility values collected from patients in TA179 and TA488. Unclear if utility values were collected from patients in TA86/209

Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, EuroQoL-5D instrument for measuring utilities		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company constructed a cohort partitioned survival cost effectiveness model, described in CS section B.3.2.6 and illustrated in CS Figure 12, reproduced in Figure 4 below. There are five health states for patients treated with first line, second line, and third line therapies and also progressed disease (PD) and death. The model has monthly cycles and a lifetime horizon (40 years).

A cohort of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST enters the model in either the avapritinib or first line treatment for ECM health states. They move to further lines of treatment according to the progression rates described in more detail in section 4.2.6.

Patients in the avapritinib arm who progress receive BSC and will not subsequently be treated with TKIs. In order to incorporate separate health utilities, BSC is modelled as three health states: SOC1/SOC2/PD. Patients in the SOC1 and SOC2 health states have the same probability of progression and death as those in the ECM arm for second and third-line respectively.

Patients in the ECM arm receive imatinib as first-line, sunitinib as second-line and regorafenib as third-line therapy. After failing third-line therapy, they will receive BSC (i.e. no further TKIs).

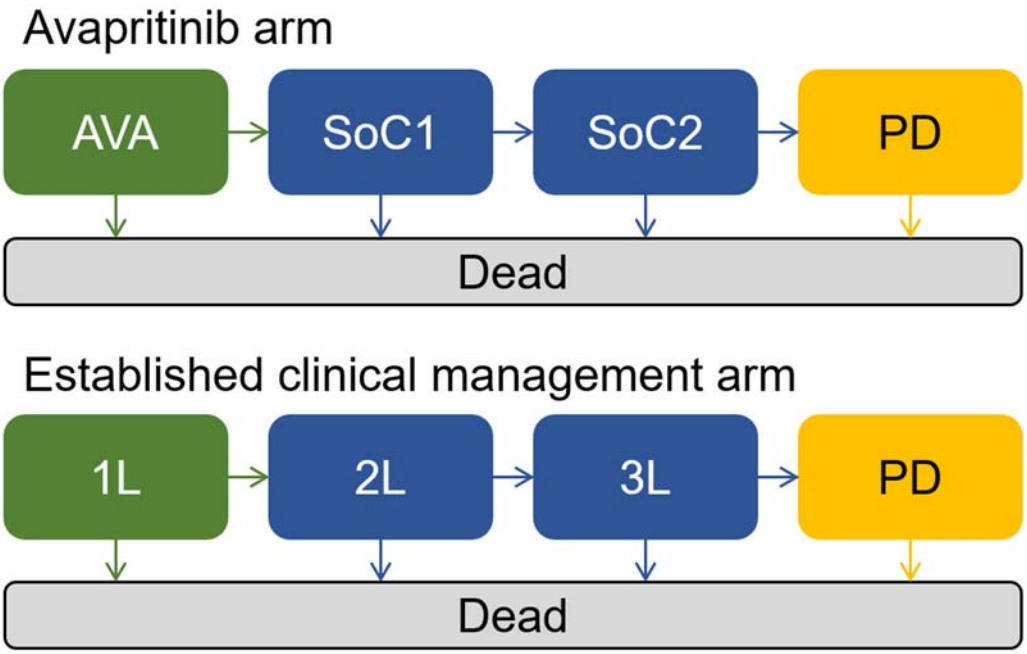


Figure 4 Structure of cost effectiveness model (reproduced from CS Figure 12)

The progression rates and death rates are taken from the NAVIGATOR study for avapritinib and BLU-285-1002 for ECM and are discussed in more detail in section 4.2.6.

The CS states "that the structure of the cost-effectiveness model is similar to the approaches used in previous NICE Technology Appraisals in unresectable or metastatic GIST" (TA86, TA179, TA488) .[11-13,39] The company note that those appraisals focused on one line of treatment (first-line, second-line and third-line GIST treatment respectively), whereas this appraisal considers the whole treatment pathway.

4.2.2.2 ERG critique of the model assumptions

The CS includes a table of modelling assumptions (CS Table 60). The ERG have added our views of these assumptions in Table 17 below.

Table 17 Company model assumptions (reproduced from CS Table 60)

Assumption	Justification	ERG comments
Clinical parameters and variables		

When a patient stops treatment with avapritinib, the benefit of avapritinib in terms of mortality is lost gradually.	• Clinical experts have suggested that the treatment effect is not lost immediately when a patient is discontinued from avapritinib and may continue for 60 months[41,42] • With no further information on the dynamics of the loss of this effect over time, linear interpolation was used	• Clinical experts advising the ERG have suggested that patients who discontinue avapritinib quickly have the same survival as those in the ECM arm.
Once a patient has lost the avapritinib treatment effect, it is appropriate to model their survival based on the ECM arm.	• Clinical experts confirmed in a survey that the overall survival of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST does not significantly differ as a result of treatment with imatinib, sunitinib, regorafenib or BSC	• We agree
The rate of further disease progression in patients with progressed disease in the avapritinib and ECM arms is the same.	• Clinical experts confirmed in a survey that the overall survival of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST does not significantly differ as a result of treatment with imatinib, sunitinib, regorafenib or best supportive care	• We agree
Health-related quality of life		
Health-state utility values from previous GIST appraisals are appropriate for decision making in this indication.	• No data are available to capture the specific HRQL of patients with this mutation • 100% of clinical experts consulted suggested that these values are representative • The progressive disease health-state utility value from TA179 was explored in a scenario analysis.	• We agree, however the utilities used for first-line are implausibly high (section 4.2.7).
Cost and health care resource use		
Excluding the costs of TKIs and management of adverse events, the cost of treating patients with metastatic or unresectable *PDGFRA* D842V-mutated GIST is the same as treating patients with general GIST.	• Excluding adverse events, there is no evidence to suggest that disease management costs will differ	• We agree
The use of branded pack costs for imatinib is appropriate.	• Generic imatinib is not currently approved by the EMA for use in GIST treatment. See CS section **Error! Reference source not found.**	• We agree

The first-line, second-line and third-line TKIs used in the treatment of patients with unresectable or metastatic GIST cost the equivalent to imatinib, sunitinib and regorafenib, respectively.	• In a survey of clinical experts, the majority of participants confirmed that, excluding patients who receive experimental therapies via clinical trials, compassionate use programmes or other means, patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in England and Wales are treated with imatinib, sunitinib and regorafenib, with most indicating that these would be used as first-, second- and third-line therapies, respectively, despite the lack of efficacy of these treatments • The mix of first-line therapies received by patients in the BLU-285-1002 study was explored in a scenario analysis	• Clinical advice to the ERG suggested that patients would not receive these therapies due to the lack of efficacy.

ERG conclusion

The three-state partitioned survival model is a standard modelling approach and has been applied in previous NICE appraisals for treatments for GIST. The company have adapted this approach to incorporate more lines of treatment. We consider that the model structure and partitioned survival approach is appropriate.

4.2.3 Population

The population included in the cost-effectiveness model is adult patients with unresectable or metastatic GIST with the *PDGFRA* D842V mutation. The population used in the economic model reflects the marketing authorisation and is in line with the NICE scope.

The ERG note that patients in the NAVIGATOR study had previously received TKIs, whereas the modelled population is assumed to have not previously received TKIs. The CS reports (CS Table 7) that "[redacted]% of patients had received prior treatment with imatinib (first line), [redacted]% had received prior treatment with sunitinib (second line) and [redacted]% had received prior treatment with regorafenib (third line). [redacted] patients ([redacted]%) had not received any prior TKI therapy". Although not explicit in the CS, we believe that all TKI use reported in NAVIGATOR would have been for unresectable or metastatic disease (i.e. not including adjuvant therapy), as explained in section 3.2.1.3 above.

The frequency of prior imatinib, sunitinib and regorafenib use (Table 5) was higher in the NAVIGATOR and BLU-285-1002 studies than would be expected in UK clinical practice. The company also provided a scenario analysis that used the study by Cassier et al[24,25] for the effectiveness of the ECM arm.

ERG conclusion

There is an inconsistency in the patient population between the economic model and the NAVIGATOR and BLU-285-1002 studies with regard to prior TKI use. The prior TKI use in these studies does not reflect UK clinical practice.

4.2.4 Intervention and comparators

The economic model compares the cost effectiveness of avapritinib versus ECM (consisting of first-line line imatinib, second-line line sunitinib and third-line regorafenib, followed by BSC). The CS states that the TKI treatments in the ECM arm have a lack of efficacy in this population with very low overall response rates and this was confirmed by the company's clinical experts. Clinical experts advising the ERG agreed and commented that for this reason few patients would receive TKIs in clinical practice. They estimated 20% of patients would receive imatinib and fewer than 10% of patients would receive sunitinb and regorafenib (although these estimates are uncertain). The ERG base case (discussed in section 6) assumes fewer patients receive these treatments in the ECM arm as suggested by our clinical experts.

ERG conclusion

The intervention (avapritinib) and the comparator (ECM comprising of first-line imatinib, second-line sunitinib and third-line regorafenib, followed by BSC) match the decision problem. However, in clinical practice not all patients would receive all the TKI treatments in ECM.

4.2.5 Perspective, time horizon and discounting

In the company's economic analysis, direct health effects of treatments are modelled and costs are estimated from the perspective of the NHS and Personal Social Services (PSS). Costs and outcomes are discounted at 3.5% in the base case (as recommended by NICE guidance[43]) and 0% discount is applied in scenario analyses.

In the base case, costs and QALYs are estimated over a lifetime time horizon (40 years). The cost-effectiveness results for alternative time horizons of 6 and 10 years are considered in scenario analyses and the model results are sensitive to changes in the time horizon.

The ERG agree that the lifetime time horizon adopted by the company in their base case is appropriate and in line with NICE guidelines.[43] The discounting rates and perspective used in the economic analysis are also consistent with NICE guidelines.

4.2.6 Treatment effectiveness and extrapolation

The CS notes that survival data in the NAVIGATOR are immature (median OS not reached) and therefore extrapolation is necessary to model mean survival. OS, PFS and ToT use the datasets from NAVIGATOR IPW for avapritinib and BLU-285-1002 for ECM. The company also provided a scenario analysis that used the study by Cassier et al[24,25] for the effectiveness of the ECM arm. ECM consisted of TKIs and BSC. The method for IPW is discussed above in section 3.5.3**Error! Reference source not found.**. The extrapolations for OS, PFS and ToT are discussed in more detail in the following sub-sections.

The company considered the visual fit of the survival extrapolation against the Kaplan-Meier data; the plausibility of the log-cumulative hazard plots, conditional probability plots, and the 1-, 2- ,5- and 10-year survival estimates; and the goodness-of-fit statistics, i.e. Akaike information criterion (AIC) and Bayesian Information Criterion (BIC). Base case survival results were validated against the opinions of UK clinical experts. The survival curves used in the model for each arm are shown in Table 18.

Table 18 Survival models used in the company base case for PFS, OS and ToT

Treatment arm	PFS	OS	ToT
Avapritinib	Weibull	Log-normal	Gompertz
ECM	1L Weibull; 2L Log-logistic; 3L Gompertz	Weibull	Uses PFS

4.2.6.1 Overall survival for patients receiving avapritinib

Modelling approach – censoring OS data for discontinuation

The OS for the avapritinib arm is estimated by combining survival estimates for patients who are on treatment and those who have discontinued treatment.

For those on treatment, the company fitted survival models to the OS IPW adjusted Kaplan-Meier data from NAVIGATOR, with events censored for discontinuation (see section 3.5.3 for more discussion of the IPW adjustment). The survival of patients who have discontinued treatment is modelled based upon the survival of patients who had received ECM, adjusted for the time since avapritinib discontinuation.

The ERG consider that the approach taken to estimate OS for avapritinib by combining the survival of those still on treatment and those who have discontinued treatment is reasonable;

however, we consider a more standard approach would be to fit survival curves to the Kaplan-Meier data for the whole population (CS Figure 6) and this approach would have a more complete dataset. For this reason, the ERG requested more explanation of the company's rationale behind their approach and a scenario using parametric curves fitted to Kaplan-Meier data without censoring for discontinuation (clarification response B1). The company provided more explanation on their approach for modelling OS. They state that this approach was taken to build a link between ToT and OS in order to allow a gradual loss of the treatment effect to be explicitly modelled. The company fitted parametric curves to the OS Kaplan-Meier data without including censoring for discontinuation (as requested by the ERG). The ICER for avapritinib versus ECM increased significantly for this scenario, compared to their base case assumption. Whilst fitting OS to the uncensored Kaplan-Meier data is preferable to the ERG, we have continued to use the company model in the ERG base case but corrected the OS extrapolation by varying the treatment waning duration.

Assumption of treatment waning

The company assume that the treatment effects of avapritinib persist after treatment discontinuation, with a gradual loss of treatment effect over 60 months after discontinuation. The CS states that clinical experts supported this assumption, but does not provide a rationale (e.g. whether the assumption reflects avapritinib's mechanism of action) and does not provide survival data over a long enough time period to validate this assumption. Based on the advice of our clinical experts, we do not consider the company's assumption of persistence of treatment benefits for avapritinib for five years to be appropriate. Our experts' view is that the risk of death for patients discontinuing avapritinib would rapidly increase to a similar risk as the ECM arm. We explore the impact of this assumption on the cost-effectiveness results in the ERG scenario analyses (discussed in section 6).

Curve fitting

The Kaplan-Meier plot for those patients on treatment is shown in CS Figure 13. The visual fit of the survival models against the Kaplan-Meier IPW adjusted plot is shown in CS Figures 14-16 and the statistical fit is shown in CS Table 34. The CS states that "given the low number of events in the Kaplan-Meier data, it is difficult to evaluate the fit of the parametric models". The log-normal model is used in the base case and this was supported by the company's clinical experts. We have a few concerns with the company's approach, as discussed below.

Firstly, NICE DSU guidance 14[44] states that the same distribution would be appropriate for both treatment arms. We therefore suggest the Weibull (which is used in the ECM arm) is a better survival model to use for avapritinib OS. Changing the distribution used for OS from the log-normal to the Weibull has a minimal effect on the cost effectiveness results. The ERG uses the Weibull model for avapritinib OS in the ERG base case in section 6.

Second, whilst the model fit for patients on treatment appears reasonable against the IPW-adjusted Kaplan-Meier data censored for discontinuation (CS Figures 14-16), the modelled OS for avapritinib differs from the IPW-adjusted Kaplan-Meier curve (CS Figure 6). In response to clarification, the company compared the OS Kaplan-Meier plot without censoring for discontinuation with the modelled OS (Clarification response Figure 14). They acknowledge that the modelled OS deviates from the OS Kaplan-Meier data (see Figure 7). The company, however, suggest that this is because NAVIGATOR is expected to underestimate the survival outcomes that would be observed in clinical practice.

We note that the discrepancy between the modelled and observed OS is largely because of the assumption that treatment effects persist beyond treatment discontinuation. As noted above, we do not support this assumption. We ran the model with differing waning durations and concluded that a waning duration of 1 month gives a close fit to the observed OS data. Therefore in the ERG base case (section 6) we have reduced the waning duration to 1 month and varied the waning duration in scenario analyses. Figure 5 shows the modelled OS compared to the observed data and the ERG's suggested approach with a waning duration of 1 month and Weibull OS distribution for avapritinib.

[redacted]

Figure 5 Avapritinib OS estimates for the company base case compared with KM data and the ERG's suggested approach

4.2.6.2 Overall survival for patients receiving ECM

The company use the IPW-adjusted BLU-285-1002 OS dataset for ECM. CS Figures 17 to 19 show the OS Kaplan-Meier data from BLU-285-1002 compared to the parametric models fitted. The AIC and BIC statistics are shown in CS Table 36. The CS states that "the Weibull parametric curve is applied at base case in the model because it has the best statistical fit as well as good visual fit to the observed data and in the long term." Table 19 shows the modelled OS for ECM compared to the observed Kaplan-Meier data. CS Table 35 shows the survival estimates for the other distributions.

Table 19 Modelled OS compared to IPW-adjusted KM survival data

Time	BLU-285-1002[a]	Company base case model
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]

[a] CS Table 17

The ERG agree the Weibull is an appropriate distribution for OS in the ECM arm and provides a good fit to the observed data. We also agree that the exponential shows a reasonable visual and statistical fit to the observed data. We have used the exponential model for OS in the ECM arm in our ERG sensitivity analyses (section 6).

4.2.6.3 Progression-free survival for patients receiving avapritinib

The best AIC and BIC statistics for IPW-adjusted PFS for avapritinib were for the Weibull and exponential models. CS Figures 20 to 22 show the Kaplan-Meier data from NAVIGATOR compared to the parametric models fitted. The AIC and BIC statistics are shown in CS Table 40. The CS states that both of these showed reasonable statistical fits. The Weibull model was used because "the probability of progression is not expected to increase with time for patients treated with avapritinib". The exponential is presented as a scenario analysis (CS Table 64). Table 20 shows the modelled PFS for avapritinib compared to the observed data. We agree with the approach taken by the company and that there is a reasonable fit to the observed data.

Table 20 Modelled PFS compared to IPW-adjusted KM survival data

Time	NAVIGATOR IPW [a]	Company base case model
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
[a] CS Table 19		

4.2.6.4 Progression-free survival for patients receiving ECM

First-line imatinib treatment

CS Figures 25 to 27 show the IPW-adjusted PFS Kaplan-Meier data from the BLU-285-1002 study for first-line imatinib treatment compared to the parametric models fitted. The AIC and BIC statistics are shown in CS Table 43. The CS states that each model presents a similar fit to the PFS Kaplan-Meier data The best AIC and BIC statistics were for the Weibull and exponential models. The Weibull model was used as it "had the best statistical fit as well as good visual fit to the clinical data." The exponential is presented as a scenario analysis (CS Table 64). Table 21 shows the modelled PFS for the first-line TKI within ECM compared to the observed data. We agree with the approach taken by the company and that there is a reasonable fit to the observed data.

Table 21 Modelled PFS compared to IPW-adjusted KM survival data

Time	IPW BLU-285-1002 [a]	Company base case model
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
[a] CS Table 19		

Second-line sunitinib treatment

Figures 21 to 23 in CS Appendix O show the PFS Kaplan-Meier data from the BLU-285-1002 study for second-line sunitinib treatment compared to the parametric models fitted. The AIC and BIC statistics are shown in Table 62 in CS Appendix O. The CS states that each model shows a similar visual fit to the Kaplan-Meier data and the company's clinical expert suggested the log-logistic distribution was the most realistic and this was used in the company's base case. The exponential and Weibull distributions had the best statistical fit.

We disagree with the choice of the log-logistic distribution and suggest that the Weibull would be a better model to use as it is consistent with the first-line model and provides a better statistical fit. We have used the Weibull model for second-line sunitinib PFS in our ERG base case (see section 6).

Third-line regorafenib treatment

Figures 24 to 57 in CS Appendix O show the PFS Kaplan-Meier data from the BLU-285-1002 study for third-line treatment compared to the parametric models fitted. The AIC and BIC statistics are shown in Table 65 in CS Appendix O. The exponential and Weibull had the best statistical fit. The Gompertz distribution is used in the company's base case "because a decreasing probability of progression over time was considered clinically plausible, and the clinical expert consulted suggested that the resulting overall survival estimates (which rely on the choice of PFS curves for the ECM arm) were appropriate". We disagree with the choice of the Gompertz distribution and suggest that the Weibull would be a better model to use as it is consistent with the first-line model and provides a better statistical fit. We have used the Weibull model for third-line regorafenib PFS in our ERG base case (see section 6).

4.2.6.5 Time on treatment

ToT for avapritinib was based on the NAVIGATOR IPW data (CS Figure 28). For ECM, the model uses PFS for a proxy for ToT (clarification response B7).

CS Figures 29 to 30 show the visual fit of the parametric models to the observed data for avapritinib. The AIC and BIC statistics are shown in CS Table 46. The exponential and Weibull distributions had the best statistical fit. However, the Gompertz distribution is used as the "company's clinical expert suggested that the model using Gompertz extrapolation of avapritinib provided clinically plausible results." We disagree with the choice of the Gompertz distribution for ToT for avapritinib. We suggest that the Weibull would be a better model to use as it is consistent with the model used for PFS and provides a better statistical fit to the observed data.

The company provide an explanation for their approach to the calculation of ToT in clarification response B9: "The ToT used censors for death and progression in order to isolate the probability of discontinuing from avapritinib treatment. This allows it to be used independently of the probabilities of death and progression of disease." Therefore the company have adjusted ToT by scaling using the percentage remaining alive who are on

treatment by OS. The equation in column CN of the "Markov Avapritinib" model sheet is provided below for clarity:

$$E(c(AVA)_t) = \%\ alive \times \%\ on\ trt \mid alive \times 1\ month\ cost\ of\ AVA$$

As with OS, we believe it would be more straightforward and transparent to fit parametric curves to the observed Kaplan-Meier for ToT. A more complicated approach is more likely to introduce errors or bias. The estimates of ToT in the economic model do not show a good fit to the observed ToT in the NAVIGATOR IPW data (see **Error! Reference source not found.**) and we believe that the cost of avapritinib has been underestimated.

In order to produce a better fit with the observed ToT and for consistency with ECM, in the ERG base case (section 6) we set ToT for avapritinib to be equal to PFS. The ToT using the ERG approach compared with the company base case and the IPW adjusted Kaplan-Meier data are shown in Figure 6.

[redacted]

Figure 6 Modelled ToT for avapritinib compared to IPW adjusted KM data

4.2.6.6 Adverse events

Adverse events for the avapritinib arm are included in the economic model for Grade 3+ all-cause adverse events with incidence ≥ 2%, as measured in the 300/400 mg dose group (CS Table 47). Adverse event data for avapritinib are from all patients in NAVIGATOR study, not restricted to those with the *PDGFRA* D842V mutation. The CS states "there is no clinical

evidence to suggest that AEs would occur more frequently in patients with or without the *PDGFRA* D842V mutation; 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." The ERG's clinical experts agreed with this assumption.

The most frequent Grade 3 adverse event was anaemia ([redacted]%), with the remaining Grade 3 events occurring in < 7% of patients. Adverse events for the first-, second-, and third-line components of ECM are shown in CS Table 48.

Adverse events were incorporated by using the cycle probability of each adverse event. In the base case, the impact of adverse events was incorporated by estimating weighted average disutilities and costs per patient, as described below in sections 4.2.7.3 and 4.2.8.3.

ERG conclusion

- The methodology used to extrapolate OS, PFS and ToT for the economic model is generally appropriate and consistent with NICE recommended methodology.
- We disagree with the company's assumption that treatment effects persist up to five years. Including this assumption leads to a large discrepancy between the OS estimates in the model and the observed OS data.
- We disagree with the choice of the log-normal model for OS for the avapritinib arm and prefer using the Weibull model.
- We prefer the Weibull model for PFS for the ECM arm for the second-line and third-line treatments. The estimates of ToT in the economic model provide a poor fit to observed ToT. To produce a better fit with the observed ToT and for consistency with ECM, we assume ToT for avapritinib to be equal to PFS. We view that the Weibull is a better model for ToT for avapritinib.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review from database inception until January 2020 aiming to identify health related quality of life (HRQoL) studies on patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST (CS section B.3.4.3 and CS Appendix H). The company searched the same databases and applied the same

methodology used to identify cost-effectiveness studies (section 4.1). The inclusion and exclusion criteria used in the review are detailed in CS Appendix Table 36.

The systematic review did not identify any relevant HRQoL studies assessing patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST but identified 18 studies assessing the overall unresectable or metastatic GIST population (CS Appendix Figure 6 and CS Appendix Table 37). Of these, three were for NICE Technology Appraisals for avapritinib comparators[11-13,39] and the remaining studies were not conducted from a UK perspective and/or reported the same utility data used in the NICE appraisals. The three NICE Technology Appraisals[11-13,39] informed the health state utility values used in the company's submission (section 4.2.7.2 below).

The ERG identified two additional studies presenting relevant utility evidence which were not included by the company.[45,46] However, both of them reported the same utilities as the company.

4.2.7.2 Health state utility values

Health state utility values were informed by previous NICE appraisals for imatinib, sunitinib and regorafenib in the treatment of unresectable or metastatic GIST.[11-13,39] In TA86/TA209 (imatinib), three clinicians answered a questionnaire to map patients' ECOG performance from the B222 trial[29] to EQ-5D. In TA179 (sunitinib) and TA488 (regorafenib), EQ-5D data were collected from patients in the A6181004[47] and GRID trials,[48] respectively. Utility values from the three previous appraisals were derived using UK preference scores. The ERG notes that the health state utility values collected from TA179 and TA488 are consistent with the NICE reference case[43] but we are unclear whether utilities from TA86/TA209 were derived directly from patients.

Previous NICE Appraisals for imatinib,[11,39] sunitinib,[12] and regorafenib[13] noted the following:
TA86/TA209: The Committee considered the utility value for the progression-free imatinib/sunitinib arm (0.935) questionable and implausibly high.
TA179: The ERG considered the source of utility values appropriate. The TA179 ERG raised some uncertainty about the utility of 0.577 for patients in progressive disease, but the ICER was insensitive to this. The NICE Appraisal Committee had the same uncertainty as the ERG regarding the progressive disease utility but agreed that the ICER was rather insensitive to variations in the utility values and therefore considered the utility values adequate.

TA488: The ERG considered the source and instrument used to measure utility values appropriate and used the same utility values as the company in their base case. The NICE Appraisal Committee accepted the company and the ERG base case utility values.

Table 22Table 22 presents the health state utility values used in the company's base case analysis in the present appraisal. We note that this set of utilities was assessed by five clinical experts advising the company, who reportedly agreed these values to be reflective of patients with unresectable or metastatic GIST in UK clinical practice. To assess the impact of utilities on the overall cost effectiveness results, the company also conducted a scenario analysis using an alternative progressive disease utility value, from TA86/209[11,39] and TA179[12] (CS Table 64). The ICER increased less than £1,000 for this analysis.

Table 22 Health state utility values used in company's base case analysis

Health state	Utility value, mean (SE)	Source	ERG comment
AVA/1L	0.935 (0.094)	TA86/TA209[11,39]	Utility value from the progression free health state for the imatinib / sunitinib arm of TA86/TA209.
SOC1/2L	0.781 (0.078)	TA179[12]	Utility value from the progression free health state from the best supportive care arm of TA179.
SOC2/3L	0.767 (0.077)	TA488[13]	Utility value from the progression free health state from the entire cohort, measured at baseline and not split by arm, of the GRID trial[48] [a]
Progressive Disease	0.647 (0.065)	TA488[13]	Utility value from the progressive disease health state from the entire cohort of the GRID trial[48] [a]
Table reproduced from CS Table 50 AVA: avapritinib; 1L: first line; 2L: second line; 3L: third line; SOC1/SOC2: standard of care [a] In the GRID trial, EQ-5D-3L was administered to collect HRQoL data for PFS and PD health states of patients receiving either regorafenib 160mg or placebo, plus BSC. The GRID trial reports utilities for the entire cohort and also split by treatment arm.			

We note that the utility value for the first line health state (AVA/1L) is higher than the UK population norm for this group. According to Ara and Brazier,[49] the utility of this age group is 0.822. In line with the NICE Appraisal Committee's assessment of TA86/TA209 (see section 4.2.7.2), the experts who provided clinical advice to the ERG also considered the first line

utility value an overestimation, stating that patients in this health state would at best experience a quality of life equal to the general population (but likely to be lower). We therefore used the utility value of 0.822 for the first-line health state in our base case analysis (see section 6).

We also note that the utility data informing SOC2/3L were collected at baseline from the entire cohort of the GRID trial,[48] pooling the regorafenib and placebo arms. We recognise that measuring HRQoL at baseline does not capture the effect of regorafenib or placebo in the management of the disease. However, we agree that the utility value used by the company for SOC2/3L is acceptable.

In general, the ERG agree with company's approach to estimate health state utility values (except for the utility value for first-line PFS) and consider that they were informed by appropriate sources.

4.2.7.3 HRQoL data from the VOYAGER study

In response to ERG clarification question B6, the company provided HRQoL data from the VOYAGER study as supplementary evidence. The VOYAGER study is an ongoing open-label, randomized, phase 3 study of avapritinib versus regorafenib in patients with locally advanced, unresectable or metastatic GIST previously treated with imatinib and one or two other TKIs. The ERG note that the HRQoL was collected as an exploratory endpoint using the EQ-5D-5L questionnaire, but no other details of HRQoL data collection were reported by the company. EQ-5D-5L data for the mutated subgroup (*PDGFRA* D842V) is based on a limited number of patients ([redacted] for avapritinib and [redacted] for regorafenib), which the company argue to be not representative of the whole unresectable or metastatic *PDGFRA* D842V population and we agree. Nonetheless, the ERG consider the HRQoL data from the VOYAGER study relevant since it is the most recently available data coming from a large sample of patients with unresectable or metastatic GIST ([redacted] patients treated at third-line and [redacted] at fourth-line), although mostly without the *PDGFRA* D842V mutation, and this is the only study collecting quality of life data from patients treated with avapritinib. Therefore, we conducted a scenario analysis using the utility values for the overall GIST population from the VOYAGER study (see section 6). Table 23 presents the mean baseline utilities for the overall GIST population from the VOYAGER study - third line utility values from the VOYAGER study ([redacted]) were used in SoC2/3L health state and the fourth line ([redacted]) in the PD health state. The company reported the baseline values, stating that they are the most appropriate for the economic model because "there were no trends identified in utility values

over time, especially when removing time points with less than 5 patients measured" and, contrarily to baseline, follow-up values can introduce bias "as patients progress and drop out of the analysis, leaving behind the healthiest patients."

Table 23: Mean baseline utilities for avapritinib and regorafenib treated patients at third or fourth line (ITT population)

	Patients treated at third line			Patients treated at fourth line		
	Avapritinib n=198	**Regorafenib n=187**	**Total n=385**	**Avapritinib n=30**	**Regorafenib n=32**	**Total n=62**
Utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from Table 3 of Supplementary health-related quality of life data from the VOYAGER study.

ERG conclusion

Whilst the VOYAGER data are relevant (as the only study that provides HRQoL data directly for avapritinib), they are based on a very small sample size for the PGDFRA D842V mutation subgroup. Therefore, we consider it appropriate to include the utility data obtained from this study in a scenario analysis (as shown in section 6) rather than in our preferred base case.

4.2.7.4 Adverse event utility decrements

The company included utility decrements associated with adverse events of grade 3-4 (CS Table 49) and assumed that adverse events of grade 1-2 have no disutility. The most common adverse events of grade 3-4 (>20%) are anaemia (reported by [redacted]% of patients receiving avapritinib), dermatitis/rash and hypertension (reported by [redacted]% and [redacted]% of patients receiving regorafenib, respectively) (CS Table 47 and Table 48).

Utility decrements are based on published articles and previous NICE appraisals. The ERG were unable to reconcile the utility decrement of hypertension with the corresponding source.[50] In clarification response B10, the company provided more details on the source of this utility decrement, which is Table 75 of the review of TA176 and partial review of TA240 for first line treatment of metastatic colorectal cancer.[51] We note that the cited table reports the adverse event utility decrements used in the Merck Serono model, in which hypertension was informed by Doyle et al.[50] However, we are unable to find a utility decrement for hypertension in the study of Doyle et al.[50] We identified a study reporting an alternative utility decrement value (0.153) for this adverse event.[52] This utility decrement is, however,

considerably higher than the value used in the company's submission (0.069) and we note that hypertension mainly occurs in patients receiving regorafenib. We believe that the alternative value will likely have a small impact on the model results, and that the utility decrement from the company's submission provides a more conservative approach (i.e. likely to favour the comparator).

When a suitable source to estimate a utility decrement was not found for an adverse event, the company assumed utility decrements from similar conditions or, when none were available, the maximum of the other utility decrements for the adverse events was assumed. This is a conservative assumption, because patients treated with avapritinib experienced a higher rate of all adverse events to which the maximum utility decrement was applied except two (abnormal liver function and haemorrhage).

A considerable number of patients receiving avapritinib experienced cognitive effects ([redacted]%) - memory impairment, cognitive disorder, confusional state and encephalopathy. However, the company only report a utility decrement for the confusional state, in which the maximum utility decrement was used (0.200), because this is a Grade 3-4 adverse event. The ERG note that the other cognitive adverse events are mild and/or occur in few patients (<2%), therefore are unlikely to influence HRQoL. We consider that the company have appropriately explored the impact of this special interest group of adverse events in HRQoL of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST.

The mean duration of adverse events in the model is seven days (CS section B.3.4.4), informed by a previous NICE appraisal (TA349)[53] and by the study of Freeman et al.[54] The clinical experts advising the ERG agreed that this period is appropriate.

4.2.7.5 Age-related utility decrements

The company account for utility decrements related to age by using the algorithm provided by Ara and Brazier.[49] We agree that this is appropriate and it is recommended by NICE DSU Technical Support Document 12.[55]

ERG conclusion

The company's review of HRQoL evidence is robust and relevant to the decision problem. The approach to estimate health state utility values, adverse events and age-related utility decrements is appropriate and consistent with the NICE reference case. However, we consider the utility values for first line treatment to be implausible

and prefer to use the UK population norm for the first-line health state. Although the ERG is not aware of the details of HRQoL data collection in the VOYAGER study, we consider that this study reports relevant HRQoL data for the unresectable or metastatic GIST population. Therefore, we conducted a scenario analysis using the utility values for the overall GIST population from the VOYAGER study for the SoC2/3L and PD health states.

4.2.8 Resources and costs

The costs included in the economic model consist of drug acquisition for first-line and subsequent treatments, health state management cost, costs for managing adverse events and terminal care costs incurred at the end of life.

The company conducted a comprehensive literature search to identify costs and resources used in the treatment and management of unresectable or metastatic GIST. The original search was completed on 5th December 2019. The search was limited to those studies published after 2009. Details of the search strategy and eligibility criteria are shown in CS Appendix I. The same study selection methodology was applied as the systematic literature review of published cost-effectiveness studies (section 4.1 above and CS Appendix G.2). The searches identified one study by Schoffski et al.[56] in which the core population was patients with unresectable or metastatic GIST with a *PDGFRA* D842V mutation. Schöffski et al. evaluated the financial impact of imatinib palliative therapy in metastatic GIST patients in Belgium, and the potential cost saving by a tailored use of imatinib based on genotyping. A further 20 studies for patients with unresectable or metastatic GIST were identified (CS Appendix I Table 45).

The resources used in the company's model were largely based upon those used in the Technology Appraisal for regorafenib for unresectable or metastatic GIST (TA488).[13]

4.2.8.1 Drug acquisition

The acquisition cost per pack for each drug is taken from the Monthly Index of Medical Specialties (MIMS).[57] Intended dosages were adjusted by the dose intensity observed in the treatments' trials. However, the relative dose intensity for imatinib was not reported in TA86 so the company assumed that there are no dose reductions or escalations for imatinib patients.

Avapritinib is an oral treatment and is licensed at 300mg QD. It is available at doses of 100 and 200 mg but all doses have the same cost. The list price of avapritinib is £26,666.67 for

30 tablets. Avapritinib is supplied to the NHS with a confidential patient access scheme (PAS) respectively.

The dosing, frequency and unit costs of the drugs are shown in Table 24 (CS Tables 51 to 55). Sunitinib has a PAS where the first six weeks of a treatment cycle are free and regorafenib has a confidential PAS. The company has reported all analyses using the list price of the comparator treatments and the PAS price for avapritinib. The ERG have replicated the company's analyses using the comparator treatment PAS prices in a separate confidential appendix to this report.

Table 24 Dosing, frequency and unit costs per administration for intervention and comparator

Drug	Daily dose	Number of capsules per pack	Pack price	Dose intensity	Cost per model cycle (1 month)
Avapritinib	300 mg	30	£26,666.67	[redacted]	[redacted]
Imatinib	400 mg	30	£1,133.41	100%	£1,149.94
Sunitinib	50 mg	28	£3,138.80	97%	£2,206.45
Regorafenib	40 mg	84	£3,744.00	87%	£3,540.84

As discussed in section 4.2.4, clinical experts advising the ERG commented that not all patients would receive all treatments in the ECM arm and that very few patients would receive second-line sunitinib and third-line regorafenib (<10%). The ERG base case (section 6) therefore assumes fewer patients receive these treatments (20% of patients receive imatinib, and 10% of patients receive sunitinib and regorafenib) in the ECM arm. For further details, refer to section 6.

4.2.8.2 Health state unit costs

The resource use and unit costs of the progression-free and progressed disease health states are shown in CS Tables 56 and 57. The CS states that health care resources for unresectable or metastatic GIST with the *PDGRA* D842V mutation are unlikely to significantly differ from general unresectable or metastatic GIST population. The health care resources were taken from the regorafenib Technology Appraisal (TA488) [13] and cost values were taken from NHS reference costs (2018-19).[58] The resource use in TA488 were based upon a survey conducted in 2013 involving 15 physicians in England and Wales. The

health care resource costs consist of one-off costs of tests taken by a proportion of patients before treatment and regular resource use per patient including pain management. Resources consist of CT and MRI scans, liver function and blood tests and outpatient visits. The one-off costs were £575.08 and £456.47 for patients in the progression-free and progressed disease health states respectively. The regular resource use costs were £217.86 and £247.32 per model cycle for patients in the progression-free and progressed disease health states, respectively.

Clinical experts advising the ERG agreed that there would be no difference in resource use between patients with this mutation and the general unresectable or metastatic GIST population and that the resource use estimates in the model are appropriate. The ERG note that the cost for an outpatient care visit in NHS reference costs was £194.17 rather than £190.64 used in the CS and company model. We obtained this value from NHS reference costs 2018/19, CL tab, currency code WF01A, service code 370, service description: Medical oncology.This was corrected in the ERG analyses (section 6).

The ERG's clinical experts also suggested that some patients with progressed disease would have fewer investigations, such as patients on palliative care. Patients receiving palliative care may transfer from hospital to hospice, so would be followed up less intensively. The experts suggested that around two thirds would continue to have regular follow-up investigations and around one third would not. We have changed resource use for these patients in the ERG analyses to the values suggested by our clinical experts (section 6).

4.2.8.3 Cost of terminal care

The company's model includes a cost of end-of-life care of £9,144.20 based upon TA488 (CS Table 59) and inflated to 2018/19 prices using the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[59] The original cost was taken from a study by Abel et al.[60] that presents end-of-life costs for a cohort of hospice patients in South West England. The study estimated that 16% of patients die in hospital and 84% die outside of hospital. The ERG's clinical advisors agreed with these estimates.

4.2.8.4 Adverse event costs

The model includes the costs of managing grade 3+ adverse events. For each model cycle, the cost of the adverse event was multiplied by its probability by cycle and the proportion of patients on treatment. The unit costs used for the management of adverse events were

taken from the latest NHS reference costs 2018/19.[58] The unit costs of the management of adverse events are shown in CS Table 58. For several of the adverse events there was no detail of the HRG code used and the ERG requested further information on these. The company provide further information on these in clarification response B5.

ERG conclusion

Fewer patients would receive TKIs in the ECM arm than assumed in the company's model. The ERG have concerns on the dose intensity used for the comparator treatments. We consider the dose intensity should be similar between the TKIs and avapritinib.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company present their base case results for avapritinib versus ECM in CS Section 4.3.8. These results, reproduced below in Table 25, show that avapritinib provides a mean QALY gain of [redacted] for an additional mean cost of [redacted] : giving an incremental cost-effectiveness ratio of £49,996 per QALY.

The cost-effectiveness results presented in the CS include a confidential PAS price for avapritinib but do not include existing PAS discounts for the comparators (sunitinib and regorafenib for the ECM arm). The results including all agreed PAS discounts for comparators as well as the company's proposed price discount for avapritinib are presented in a confidential addendum to this ERG report.

Table 25 Cost effectiveness: Company's base case (discounted)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]	-	-	-
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	£49,996
Source: CS Table 61					

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company summarise the parameters and ranges included in the deterministic sensitivity analysis (DSA) in the CS Appendix M. The DSA are presented as a tornado plot in CS Figure 33. The plot shows that the baseline patient age, discount rates and health state utility values are key drivers of the model results. Other parameters such as management costs and HRQoL parameters for the general population also influence the results, but to a lesser extent. The DSA did not include parameters related to clinical effectiveness, except for proportion of deaths in the pre-progression stage for the Cassier ECM study. The company argue that their base case clinical effectiveness estimates are likely to be underestimates as the data from NAVIGATOR constituted a mixture of patients at different treatment lines whereas, in clinical practice, avapritinib would be used as a first-line therapy. To examine the impact of the clinical effectiveness parameters on the overall model results as well as a range of other parameters, the ERG conducted a range of sensitivity analyses, details of which are discussed in section 6.

5.2.2 Scenario analyses

The company conducted a range of scenario analyses to analyse the impact of key variables on the model outcomes in CS Table 64.

Whilst most of the scenarios did not have a significant impact on the cost effectiveness results, the use of shorter time horizons (i.e. 6 years and 10 years) had the greatest impact on model results. We extended the range of scenario analyses in ERG additional analyses, described below (see section 6).

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) on their base-case model to assess parameter uncertainty. In summary, the company assigned the normal distribution for efficacy parameters; the beta distribution for health state utilities and adverse event disutilities; and the gamma distribution for the costs and duration of adverse events. Probabilistic results are presented in CS Table 63; scatter plots in CS Figure 31; and the cost effectiveness acceptability curve (CEAC) in CS Figure 32. The company report that the PSA results are close to the deterministic results. The CS states that at a willingness-to-pay threshold of £50,000 per QALY, avapritinib had 42.4% probability of being cost-effective compared to ECM.

Whilst we consider that the company assigned appropriate distributions to the model parameters; the ERG were unable to replicate the PSA simulations. The company provided a revised version of their model with corrections in response to clarification question B4 to appropriately reflect uncertainty over the input parameters. The ERG were able to replicate the PSA in this updated version of the model.

5.3 Model validation and face validity checks

5.3.1 Company validation of their model

The company describe their approach to model validation in CS section B.3.10. They state that they conducted clinical validation of the survival estimates produced by the cost-effectiveness model, health states utilities, current and avapritinib treatment pathways, and healthcare resources used.

The key conclusions that the company drew from the validation exercise are as follows:

- Two clinical experts independently agreed with the company's estimates of PFS and OS;
- Five clinical experts agreed with the health state utilities used by the company for their base case;
- In the company's survey of clinical expects, most of the experts are reported to agree with the treatment sequences used in the company's model for the ECM arm for patients with unresectable or metastatic PDGFRA D842V-mutated GIST. Nonetheless, the company conducted a scenario analysis where they include the drug costs of additional TKIs in BLU-285-1002 study, which are not currently approved for the treatment of GIST patients in England and Wales. Further details on the mix of TKIs in BLU-285-1002 study is presented in CS Appendix Q. Including the additional TKIs did not have a significant impact on the cost effectiveness results.
- There was a lack of clinical consensus on the healthcare resources used at different treatment lines. To address this issue, the company conducted a scenario analysis where values suggested by the clinical survey results (further details in CS Appendix R) were used. This scenario increased the ICER for avapritinib versus ECM by approximately [redacted] compared to the company's base case ICER.

To check for face validity, the company compared the modelled outcomes with the clinical data censored for discontinuation or death, rather than full dataset (CS Appendix J). We reproduce these results in Table 26 below. We note that the PFS and OS estimates from the raw data (sources are in Table 26) are slightly higher than the modelled estimates. The company defends this by citing that i) OS for avapritinib is estimated using ToT, the raw data for avapritinib and raw data for ECM; and ii) this would be true when the raw avapritinib Kaplan-Meier data fails to reach median (as can be seen at different years from baseline).

Table 26 Comparison of the modelled outcomes with clinical data as reported by the company

Treatment	Data (source)	Year 1	Year 2	Year 3	Year 4	Year 5
PFS						
Avapritinib	Raw data (NAVIGATOR, IPW adjusted censored for death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Modelled data	87%	67%	48%	31%	18%
ECM	Raw data (BLU-285-1002, IPW adjusted censored for death)	6%	6%	0%	0%	0%
	Modelled data	3%	0%	0%	0%	0%
OS						
Avapritinib	Raw data (NAVIGATOR, IPW adjusted censored for discontinuation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Modelled data	99%	95%	89%	81%	70%
ECM	Raw data (BLU-285-1002 IPW adjusted)	48%	34%	19%	17%	14%
	Modelled data	45%	29%	20%	14%	11%
Source: CS Appendix J Table 46						

In response to clarification question B2, the company compared the modelled outcome of OS with the observed data from the NAVIGATOR IPW analysis and the BLU-285-1002 study, applying various durations of treatment waning (reproduced in Figure 7 below). The modelled OS curve is an overestimate compared to the OS Kaplan-Meier data from NAVIGATOR. The company argue that better survival would be expected in clinical practice when avapritinib is used first line, rather than when used at a later line of treatment as in NAVIGATOR (clarification response B1). We view that the company's argument may not be applicable for patients who have had several prior TKIs as in the case of participants in the NAVIGATOR study where they received more frequent prior TKIs than would be expected in UK clinical practice. Therefore, we treat the modelled overestimation of OS with caution and explore this further in our scenario analyses in section 6.

[redacted]

Source: reproduced from Figure 14 in clarification response B2

Figure 7 Comparison of modelled OS outcomes against clinical data

ERG conclusion

The company conducted appropriate internal validity and face validity checks. Whilst there are no previous technology appraisals in GIST population with PDGFRA D842V mutation, we view it reasonable to compare the model results in the current appraisal against three previous appraisals in GIST (including an update) i.e. TA86/TA209; TA179 and TA488, to provide some means of cross-validation.

5.3.2 ERG validation of the company's model

The ERG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checked all parameter inputs against values reported in the CS and cited sources;
- Checked the individual equations within the model;
- A range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed;
- Recoded sections within the Markov calculations for the ECM arm to check model calculations;
- Checked all model outputs against results cited in the CS, including the base case, PSA, DSA and manually ran all the scenarios.

The company model was generally well-implemented with no substantive errors in parameter inputs or coding, except two issues as discussed in section 5.3.3.

Face validity checks

We consulted our clinical experts to validate the company's assumptions relating i) the impact of survival benefit from treatment waning; and ii) likely survival estimates observed in clinical practice for patients with GIST. The observations are summarised in Table 27. We conducted scenario analyses to address our experts' opinions; see Section 6.

Table 27 Comparison of the model assumptions with ERG clinical experts' opinions

Aspect	Company assumption	ERG clinical experts' opinion
Treatment waning	After patients discontinue treatment with avapritinib, the company assume that there will be a gradual loss of treatment effect, rather than losing all survival benefits immediately.	Patients' responses to TKIs are variable. While gradual waning may be true for some patients, others may exhibit rapid progression. Our experts viewed the overall company estimate of five years for treatment waning to be too long. For patients who stopped treatments due to progression, it was highly likely that they would rapidly revert to the rate of death that would be expected in untreated patients. Generally, most patients not on treatment would die within 12-18 months.
OS estimates for the ECM arm from the company's base case	5 years: 10.7% 10 year: 3.1%	5 years: Between 5% and 11% 10 years: 0%

Cross validity checks against previous Technology Appraisals

We compared the modelled QALY estimates from the current appraisal with three previous NICE technology appraisals (including an TA update) for treatments for patients with GIST (TA86/TA209; TA179 and TA488). Despite methodological differences between the models, they provide some means of cross-validation. We note that the QALY and life year estimates from the current appraisal are [redacted] than the other available lifetime model: e.g. the QALY estimate from TA488 was 0.969 for the comparator treatment (BSC) compared to [redacted] for ECM in the current appraisal (Table 28).

Table 28 Comparison of modelled outcomes

Source (time horizon)	QALYs	QALYs	Life Years
Current appraisal (Lifetime-40 years)	Avapritinib	[redacted]	[redacted]
	ECM	[redacted]	[redacted]

Source (time horizon)	QALYs	QALYs	Life Years
TA86/TA209 (10 years) [a]	Path 1: BSC	2.397	4.154
	Path 7: Sunitinib	2.411	3.716
	Path 4: Imatinib 600 mg	4.256	5.211
	Path 3: Imatinib 600 mg, followed by sunitinib	4.286	5.032
	Path 6: Imatinib 800mg	3.635	4.506
	Path 5: Imatinib 800 mg, followed by sunitinib	3.659	4.336
	Path 2: Imatinib 600-800 mg, followed by sunitinib	4.803	5.278
TA179 (6 years)	Sunitinib	1.23	1.98
	BSC	0.73	1.21
TA488 (40 years) [b]	Regorafenib	1.733	NA
	Placebo + BSC	0.969	NA

[a] The 7 strategies represent 7 model pathways: Path 1- patients receive BSC; Path 2- treatment with escalated doses of imatinib (600 and 800mg/day) followed by sunitinib; Path 3- treatment with escalated dose of imatinib 600mg/day followed by sunitinib; Path 4- treatment with imatinib 600mg with no treatment switching; Path 5- treatment with escalated dose of imatinib 800mg/day followed by sunitinib; Path 6- treatment with imatinib 800mg; and Path 7- treatment with sunitinib

[b] Based on company's revised base case using 2017 data cut and GRID trial treatment duration;[48]
NA: Not Publicly Available; BSC: Best Supportive Care

5.3.3 ERG corrections to the company model

As previously stated, the company model was generally well-implemented, with no substantive errors in parameter inputs. The ERG, however, identified two errors in the model which are summarised below in Table 29.

Table 29 ERG corrections to the company model

Issue	Model aspect	Issue	ERG correction
1	Estimation of outpatient care visit from NHS Reference costs	The company model used an estimate of £190.17	The corrected value is £194.17 (see below Table 30).
2	PSA simulations	We were unable to replicate the company's PSA simulations.	The company addressed this issue in their response to clarification questions (for further details see clarification response B4). The ERG could replicate the PSA simulations using the revised code provided by the company.

The ERG addressed Issue 1 by re-running the analysis with the corrected value of £194.17 for an outpatient care visit. The overall impact of this change is small i.e. an increase in the base case ICER from £49,996 (company's base case) to £50,033 per QALY (see Table 30).

Table 30 Cost effectiveness results from ERG correction of Issue 1 (discounted)

Therapy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]	-	-	-
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	£50,033

We re-ran all the company's scenario analyses (presented in CS Section B.3.8.3 Table 64) with the corrected model and the results are presented in Table 31 below. The cost-effectiveness results in these scenarios are similar to those from the company's scenario analyses with the ICERs increasing minimally (approximately £100) across each of these scenarios.

Table 31 Results of the company's scenario analysis using the ERG corrected company model (discounted)

Scenario		Total costs	Total QALYs	ICER (£/QALY)
Base case (ERG corrected)	Avapritinib	[redacted]	[redacted]	
	ECM	[redacted]	[redacted]	£50,033
No discounting	Avapritinib	[redacted]	[redacted]	
	ECM	[redacted]	[redacted]	[redacted]
No discounting for outcomes	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
No discounting for costs	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Time horizon: 6 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
ECM TKIs from BLU-285-1002	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Incomplete loss of treatment benefit: 10%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Incomplete loss of treatment benefit: 20%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Post-avapritinib progression rate slowed by 10%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Post-avapritinib progression rate slowed by 20%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
End of life costs from Round et al.	Avapritinib	[redacted]	[redacted]	[redacted]

	ECM	[redacted]	[redacted]	[redacted]
PD utility from sunitinib TA	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Palliative surgery, radiotherapy, hospitalizations from clinical Survey	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Cassier et al.survival for the comparator arm	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Overall survival: Avapritinib - log-logistic	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Progression-free survival: Avapritinib - exponential	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Progression-free survival: ECM - exponential	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]

5.3.4 ERG summary of key issues and additional analyses

A full summary of ERG observations on key aspects of the company's economic model is presented in Table 32.

Table 32 ERG observations of the key aspects of the company's economic model

Issues	Features of the company model	ERG comments	ERG analysis	Priority issues to consider
Modelled decision problem				
Population	The modelled patient population is described in CS section 3.2.1.2	The model population is appropriate for the scope and the anticipated marketing authorisation. However, patients in the model are assumed to have no previous TKIs unlike patients in the NAVIGATOR and BLU-285-1002 studies. Secondly, the prior TKI use in these studies does not reflect the UK clinical practice.		HIGH (remains unresolved)
Intervention & comparators	• Intervention: Avapritinib (1st line), SoC (2nd line) and SoC (3rd line) • Comparator: ECM which comprises of imatinib (1st line), sunitinib (2nd line) and regorafenib (3rd line)	The intervention and comparators align with the NICE scope, although in clinical practice not all patients would receive all the comparator treatments. Based on the ERG's clinical advice, few patients would receive 2nd and 3rd line treatments due to lack of efficacy in this patient population combined with drug toxicity.	***ERG base case:*** For the ECM arm, 20% of patients receive 1st line imatinib, followed by 10% of patients receiving 2nd line sunitinib and 3rd line regorafenib. ***ERG scenario:*** For the ECM arm, 0% receives 1l, 2L and 3L.	HIGH
Assumptions about treatment				
Dose intensity	***Company base case:*** • Avapritinib: [redacted] • Imatinib: 100% • Sunitinib: 97% • Regorafenib: 87%	Our clinical experts view that the dose intensity is similar amongst the TKIs.	***ERG base case:*** Dose intensity of imatinib, sunitinib and regorafenib same as that of avapritinib	LOW
Model structure and framework				
Model type	Cohort partitioned survival model (CS Figure 12).	The overall model structure is appropriate, consistent with previous TA models in GIST and accurately implemented.		
Cycle length	1 month	The ERG agree with this assumption		

Half cycle correction	A half cycle correction was applied by using the mean number of patients in each health state at the beginning and end of each cycle to calculate costs and QALYs	Consistent with NICE methods guidance.		
Time horizon	40 years (patients enter the model at [redacted] years of age)	Consistent with a lifetime horizon and NICE guidance		
Clinical parameters				
Overall survival	***Treatment waning effect:*** The company's base case model assumes a gradual movement of OS hazard from the avapritinib arm to that of the ECM arm upon discontinuation from avapritinib treatment, meaning a gradual loss of treatment effect over a period of 5 years (60 model cycles).	The ERG's clinical experts advise that the company's assumption is not reflective of clinical practice (see section 4.2.6 for further details).	***ERG base case:*** Duration of treatment waning effect is 1 month ***ERG scenarios:*** Treatment waning ranging between 1 and 24 months	HIGH
	OS survival data: OS for avapritinib is based on patients who are still receiving avapritinib, i.e. the OS for this arm is censored for discontinuation	The model OS has a poor fit to the OS data in NAVIGATOR. This is corrected by changing the assumption of treatment waning.		
	Extrapolation (company's base case): • Avapritinib: Log-normal • ECM: Weibull	We agree that the Weibull is an appropriate fit for the ECM OS curve. To align with the NICE DSU methods guide,[44] both treatment arms should preferably use the same distribution (see section 4.2.6).	**ERG base case:** • Avapritinib: Weibull • ECM: Weibull **ERG scenario:** • Avapritinib: Exponential • ECM: Exponential	MEDIUM
Progression free survival	***Extrapolation:*** • Avapritinib: Weibull (base case) • ECM: - 1L: Weibull (base case); exponential (scenario) - 2L: Log-logistic (base case) - 3L: Gompertz (base case)	We agree with the extrapolation methods, but consider that the Weibull model provides a better fit to the observed data and would be more consistent with that used for 1L (see section 4.2.6).	***ERG base case:*** • Avapritinib: Weibull • ECM: - 1L: Weibull - 2L: Weibull - 3L: Weibull	MEDIUM
Time on Treatment	For the avapritinib arm, the ToT is censored for discontinuation	The method used to estimate ToT does not provide a close fit to the ToT KM data. For consistency with the ECM arm, we have set ToT equal to PFS for avapritinib (see section 4.2.6).	***ERG base case:*** We have set ToT equal to PFS for avapritinib.	HIGH

	The ToT is extrapolated using a Gompertz curve	We note that a Weibull curve provides a better statistical fit to the observed data and is consistent with the model used for PFS.	***ERG base case*:** Weibull	MEDIUM
Mortality	The model uses general population all-cause mortality rates adjusted for age and gender from UK Life tables (ONS data for 2015-2017). The excess mortality for GIST is obtained from the OS estimates.	The data for all-cause mortality are slightly out-of-date. For completeness, the ERG consider it appropriate to use the ONS data for 2016-2018.	**ERG base case:** Using ONS mortality data for the year 2016-2018.	LOW
Utilities				
Health state utilities	Company base case model estimates: • PFS 1L: 0.935 • PFS 2L: 0.781 • PFS 3L: 0.767 • PD: 0.647 Company scenario analysis: • PFS 1L: 0.935 • PFS 2L: 0.781 • PFS 3L: 0.767 • PD: 0.577	The utility for PFS 1L is implausible as this value is higher than the general population utility of 0.822. The estimates for 2L ,3L and PD appear to be appropriate	***ERG base case**:* • PFS 1L: 0.822 • PFS 2L: 0.781 • PFS 3L: 0.767 • PD: 0.647 ***ERG scenario:*** • PFS 1L: 0.822 • PFS 2L: 0.781 • PFS 3L: 0.767 • PD: 0.577	HIGH
	HRQoL data for this population are collected using EQ-5D-EL and EORTC as part of the VOYAGER study comparing avapritinib versus regorafenib.	Due to uncertainty in HRQoL estimates in this patient population, these data may provide some useful information, and hence we ran a scenario analysis with VOYAGER utility estimates.	***VOYAGER scenario:*** • PFS 3L: 0.782 • PD: 0.727	MEDIUM
	General population utility by age and gender from Ara and Brazier (2010).	The ERG agree with this assumption		
Costs and resource use				
Resources used for estimating the health state costs	All patients with progressed disease continue to receive investigations.	Patients with progressive disease on palliative care may have fewer investigations (e.g. scans and blood tests may not be necessary). Patients receiving palliative care may transfer from hospital to hospice, so would be followed up less intensively.	***ERG base case:*** Two-thirds would continue to have regular follow-up investigations and around one-third would not.	LOW
1L: first-line; 2L: second-line; 3L: third-line				

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the ERG critique of the company's model assumptions (as outlined in Table 32 above), we performed a range of additional scenario analyses (shown in Table 33 below) on the following model assumptions:

- Varying the proportion of patients receiving 1L, 2L and 3L treatments in the ECM arm;
- Same dose intensity for all the TKIs as avapritinib;
- Varying the duration of treatment waning for avapritinib;
- Extrapolating OS, PFS and ToT using different survival distributions;
- Assuming ToT for avapritinib arm as similar to PFS (i.e. same assumption as used in the ECM arm);
- Alternative sources for utilities and resource use; and
- Using updated all-cause mortality data (i.e ONS 2016-2018)

The scenarios analyses were performed on the ERG corrected company's model. We note:

- For the scenarios, the ICERs range from [redacted] (Scenario: ERG resource used for progressed disease) to [redacted] (Scenario: Duration of treatment waning at 1 month). The ICERs for avapritinib versus ECM remain above £50,000 except for one scenario (Scenario: Change in resource use for progressed disease).
- Assuming a duration of treatment waning of 1 month had the greatest impact on the cost-effectiveness results. The ICER for avapritinib versus ECM increased to [redacted] per QALY. Using PFS as a proxy for time on treatment for avapritinib has a significant impact on the cost-effectiveness results; the ICER for avapritinib versus ECM increased to [redacted] per QALY.
- Another scenario that significantly influences the cost effectiveness results is the extrapolation of overall survival using the exponential distribution for both treatment arms to [redacted] per QALY.
- Using utility values from the VOYAGER study did not have a significant impact on the cost effectiveness results; the ICER for avapritinib versus ECM decreased minimally to [redacted] per QALY compared to [redacted] per QALY in the base case.

Table 33 Additional analyses conducted by the ERG on the company's base case (ERG corrected)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	Avapritinib			
	ECM			£50,033
ECM: Proportion of patients receiving 1L (20%); 2L (10%) and 3L (10%)	Avapritinib			
	ECM			
ECM: Proportion of patients receiving 1L (0%); 2L (0%) and 3L (0%)	Avapritinib			
	ECM			
Dose intensity: same for all the treatments at	Avapritinib			
	ECM			
Duration of treatment waning: 1 month	Avapritinib			
	ECM			
Duration of treatment waning: 6 months	Avapritinib			
	ECM			
Duration of treatment waning: 12 months	Avapritinib			
	ECM			
Duration of treatment waning: 24 months	Avapritinib			
	ECM			
Duration of treatment waning: 36 months	Avapritinib			
	ECM			
Duration of treatment waning: 48 months	Avapritinib			
	ECM			
Extrapolation of OS: Avapritinib (Weibull); ECM (Weibull)	Avapritinib			
	ECM			
Extrapolation of OS: Avapritinib (Exponential); ECM (Exponential)	Avapritinib			
	ECM			
Extrapolation of PFS for ECM: 1L (Weibull); 2L (Weibull); 3L (Weibull)	Avapritinib			
	ECM			
Time on treatment for avapritinib: Using PFS as proxy for ToT	Avapritinib			
	ECM			
Extrapolating time on treatment for avapritinib using Weibull	Avapritinib			
	ECM			
All cause mortality using ONS 2016-2018	Avapritinib			
	ECM			
Utility for PFS 1L 0.822	Avapritinib			
	ECM			
Utility for PD 0.577	Avapritinib			
	ECM			
Utility from VOYAGER trial (PFS 3L: 0.782; PD: 0.727)	Avapritinib			
	ECM			
Resources used for PD state based on ERG clinical advice	Avapritinib			
	ECM			

6.2 ERG's preferred assumptions

Based on the ERG critique of the company's economic model discussed in section 5.3.4**Error! Reference source not found.**, we have identified seven key aspects of the company base case with which we disagree. Our preferred model assumptions are discussed below:

1. ***Proportion of patients receiving 1st line, 2nd line and 3rd line treatments in the ECM arm:*** Advice from our clinical experts suggest that due to lack of effectiveness and risk of toxicity, GIST patients with the *PDGFRA* D842V mutation would not usually receive TKIs. Therefore, we assume in our base case that only 20% of the patients in the ECM arm would receive first-line imatinib treatment; followed by 10% of patients receiving second-line sunitinib and third-line regorafenib treatments respectively (for further discussion, see section 4.2.4).
2. ***Dose intensity****:* We assume similar dose intensity for all the TKIs in the ECM arm to that of avapritinib, i.e. [redacted] (further discussion in section 4.2.8.1).
3. ***Duration of treatment waning:*** Advice from our clinical experts is that patients are not likely to have persistence of clinical benefit for avapritinib for 5 years (section 4.2.6). The ERG assume a treatment waning period of 1 month as our preferred assumption (for further discussion, see section 4.2.6).
4. ***Extrapolation of survival curves:*** For consistency between treatment arms we prefer the Weibull distribution for the avapritinib arm (same as that of the ECM arm) to estimate OS, aligning with the NICE DSU guideline.[44] Similarly, for the PFS we use Weibull distribution for the second and third lines of ECM as this provides a better fit to the observed data and is consistent with first-line PFS (for further discussion, see section 4.2.6).
5. ***Time on treatment:*** We consider that the company's approach to fit parametric curves to the Kaplan-Meier data censored for deaths does not provide a close fit to the Kaplan-Meier data. For consistency with the ECM arm, we use PFS as a proxy for time on treatment for avapritinib (for further explanation, see section 4.2.6). For our preferred base case, we use a Weibull distribution for ToT extrapolation for this arm. This is consistent with our preferred distribution for PFS (for further discussion, see section 4.2.6)
6. ***Utility:*** For the ERG preferred base case, we assume that the utility value for the first line health state (AVA/1L) is same as that of the general UK population for this age-group, which is 0.822. We agree with the company's estimates for the remaining health states (for further discussion, see section 4.2.7)
7. ***Resource use:*** To reflect clinical practice, we assume that two-thirds of the patients in the progressed health state would continue to have regular follow-up investigations (i.e. CT scans; MRI scan; full blood count; and liver function test) and about one-third would not (for further discussion, see section 4.2.8)

In addition to the above key issues, for completeness we have also updated the model with the latest all-cause mortality data available from ONS 2016-2018 estimates.

Results from the ERG preferred assumptions

We show the cumulative impact of applying the ERG preferred assumptions to the corrected company's base case in Table 34. Incorporating the ERG assumptions has a significant impact on the overall ICER for avapritinib versus ECM, increasing the ICER from [redacted] per QALY to [redacted] per QALY. We observe that:

- The change that has the biggest impact on the cost-effectiveness results is the assumption that treatment waning is for 1 month. Using PFS as proxy for time on treatment for avapritinib and using general population utility value for first-line PFS also cause an increase in the ICER for avapritinib versus ECM.
- Incorporating the remaining of the ERG assumptions influence the ICER for avapritinib versus ECM, but to a lesser extent.

Table 34 Cumulative cost-effectiveness results for ERG's preferred model assumptions

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company base case (ERG corrected)	Avapritinib	[redacted]	[redacted]	
	ECM	[redacted]	[redacted]	£50,033
+ ECM: Proportion of patients receiving 1L (20%); 2L (10%) and 3L (10%)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Dose intensity: same for all the treatments at [redacted]	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Duration of treatment waning: 1 month	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Extrapolation of OS: Avapritinib (Weibull); ECM (Weibull)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Extrapolation of PFS for ECM: 1L (Weibull); 2L (Weibull); 3L (Weibull)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Time on treatment for avapritinib: same as PFS	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Extrapolating time on treatment for avapritinib using Weibull	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ All-cause mortality using ONS 2016-2018	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ ERG preferred utilities (PFS 1L: 0.822; PFS 2L: 0.781; PFS 3L: 0767; PD: 0.647)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
+ Resources used for PD state based on ERG clinical advice	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
ERG preferred base case	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]

Incorporating the ERG preferred assumptions lower the OS estimates for the avapritinib arm significantly, compared to the estimates obtained from the company's base case (see Table

35). Based on the ERG assumptions, the overall survival of GIST patients with PDGFRA D842V mutation at 1 year is [redacted]; and[redacted] at 5 years. The OS estimates for the ECM arm are unchanged from the company's base case as we agree with the company's assumptions in relation to the estimation of the ECM survival estimates (as discussed previously in section 4.2.6).

Table 35 Comparison of the OS estimates between company's base case and ERG base case

Time	OS from Company's base case		OS from ERG base case	
	Avapritinib	ECM	Avapritinib	ECM
1 year	[redacted]	45%	[redacted]	45%
2 years	[redacted]	29%	[redacted]	29%
3 years	[redacted]	20%	[redacted]	20%
4 years	[redacted]	14%	[redacted]	14%
5 years	[redacted]	11%	[redacted]	11%

We present a comparison of the Markov traces for the ERG base case and company's base case showing the proportion of the cohort in each health state over time in Figure 8 and Figure 9

Figure 9. The proportions of patients in the treatment state is lower in the ERG base case compared with the corrected company's base case.

i) Company base case

[redacted]

ii) ERG preferred base case

[redacted]

Figure 8 Comparison of Markov traces for avapritinib: proportion of cohort in each health state over time

i) Company base case

[redacted]

ii) ERG preferred base case

[redacted]

Figure 9 Comparison of Markov traces for ECM: proportion of cohort in each health state over time

6.3 Scenario analyses conducted on the ERG's preferred assumptions

We performed a range of scenario analyses on the ERG base case, as shown in Table 36. Briefly, we conducted these analyses to assess the impact of changing the following model assumptions on the overall cost effectiveness results. Most of these scenarios are replicated from the company's scenario analyses (as previously outlined in section 5.2.2)

- Varying patients' initial age;
- Different model time horizons;
- Variations in duration of treatment waning for avapritinib;
- Inclusion of drug costs of the additional TKIs in BLU-285-1002 study, which are not currently approved for the treatment of GIST patients in England and Wales;
- Variation in the percentage of incomplete loss of treatment benefit after discontinuation for the avapritinib arm;
- Variation in the post-progression rate for the avapritinib arm;
- Using alternative sources to inform model parameters such as End of Life costs (i.e. Round et al); resource use (based on clinical survey); and utilities (VOYAGER and previous NICE TA);
- Using the Cassier study as source for comparator clinical effectiveness; and
- Assigning different survival distributions to extrapolate OS and PFS.

We note:

- The ICERs for avapritinib versus ECM range from [redacted] per QALY (Scenario: treatment waning period of 24 months) to [redacted] per QALY (Scenario: extrapolating the OS curves using exponential distribution) with the ICER above £50,000 per QALY for all the scenarios.
- The scenarios that have the greatest impact on the cost-effectiveness results are using a shorter time horizon of 6 years (ICER of [redacted] per QALY) and extrapolating the OS curves using the exponential distribution (ICER of [redacted] per QALY);
- Duration of treatment effect influences the cost-effectiveness results. For example, assuming a treatment waning period of 6 months reduces the ICER significantly to [redacted] per QALY; [redacted] per QALY for 12 months and [redacted] per QALY for 24 months, respectively;
- Using the Cassier study to inform survival for the ECM arm increases the ICER for avapritinib versus ECM to [redacted] per QALY; an increase of [redacted] from the ERG base case ICER;

- The remaining scenarios (i.e. changing patient's age, inclusion of drug costs of the additional TKIs in BLU-285-1002 study, extrapolation of PFS using exponential and incorporating utility estimates from the VOYAGER study and previous NICE TA for sunitinb have a lesser impact on the ICER for avapritinib versus ECM.

Table 36 Scenario analyses using the ERG's preferred model assumptions

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
ERG preferred model	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Initial age: 50 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Initial age: 70 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
No discounting	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Time horizon 6 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Time horizon 10 years	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Treatment waning: 6 months	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Treatment waning: 12 months	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Treatment waning: 24 months	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
ECM TKIs from BLU-285-1002	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Incomplete loss of treatment benefit after discontinuation for avapritinib arm: 10%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Incomplete loss of treatment benefit after discontinuation for avapritinib arm: 20%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Post-avapritinib progression rate slower: 10%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Post-avapritinib progression rate slower: 20%	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
End of life costs from Round et al	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
PD utility from Sunitinib TA	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Palliative surgery, radiotherapy, hospitalisations from clinical survey	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
Cassier et al survival for comparator arm	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
OS Avapritinib: log logistic	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
OS Avapritinib and ECM: exponential	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]
PFS for avapritinib and ECM: exponential	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Utility from VOYAGER trial (PFS 3L: 0.782; PD: 0.727)	Avapritinib	[redacted]	[redacted]	[redacted]
	ECM	[redacted]	[redacted]	[redacted]

6.4 ERG conclusions on cost effectiveness

The key issues in the cost effectiveness evidence are:

- company modelled outcomes provide a poor fit to observed OS Kaplan-Meier data for avapritinib,
- company modelled outcomes do not provide a close fit to observed ToT Kaplan-Meier data for avapritinib,
- health utility values for first-line treatment therapy appear to implausible,
- the economic model assumes that patients in the ECM arm all have first-line imatinib, second-line sunitinib and third-line regorafenib treatment which clinical experts advising the ERG said was not reflective of clinical practice,
- the survival models used, for OS and ToT, differed between treatment arms.

The ERG also disagree with the company with the dose intensity used for the comparator TKIs and the proportion of patients receiving investigations in the progressed health state, however these are minor issues.

The ERG base case, which corrects the aforementioned issues, with our preferred assumptions increased the ICER for avapritinib versus ECM to £[redacted] per QALY gained. The results were most sensitive to changes in the time horizon, the treatment waning duration and the survival models used for OS.

7 END OF LIFE

The CS contends that avapritinib should be considered as an end-of-life therapy. The evidence for this is presented in CS Table 30 (reproduced below in
Table 37). With ECM, life expectancy is expected to be below 24 months. Patients have a median OS as low as [redacted] months. In the base case for the economic model, mean OS for patients treated with ECM is 23.72 months.

Median OS was [redacted] in the NAVIGATOR study as the OS data are not yet mature. The economic model presented in CS section **Error! Reference source not found.**. shows that avapritinib would provide an additional [redacted] life-years for patients with unresectable or

metastatic GIST with the *PDGFRA* D842V mutation, compared with ECM (CS Appendix J.2.). We do not agree with all the assumptions made for the modelling of avapritinib. Nevertheless, even with the ERG's suggested changes, the additional life years for patients treated with avapritinib would be considerably more than an additional 3 months.

On the basis of the evidence presented in the CS, the ERG agree that avapritinib meets the requirements set by NICE to be considered as an end-of-life therapy.

Table 37 End-of-life criteria

Criterion	Data available	Reference in CS (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Mean survival:** 23.72 months **Median survival estimates:** BLU-285-1002 IPW-adjusted: [redacted] months Cassier et al., 2012: 14.7 months **24 month survival estimates:** BLU-285-1002 IPW-adjusted: [redacted] % Cassier et al., 2012: NR[25]	**BLU-285-1002** Section **Error! Reference source not found.**; Page 54 and Section **Error! Reference source not found.**, Page 136 **Cassier et al., 2012** Appendix D.1; Pages 35–36
There is sufficient evidence to indicate the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**Median survival estimate:** [redacted] **24 month survival estimate:** [redacted] % **42 month survival estimate:** [redacted] % **Incremental LY gains:** [redacted]	Section **Error! Reference source not found.**, Pages 38–40 and Appendix J.2, Page 89
Source: Reproduced from CS Table 30 LY, life year		

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9 Appendices

Appendix 1 Therapies received by patients in the Cassier study

Therapy received (overall study population) [a]	Accumulated number of TKIs	Number of patients
First line (N=10)		
Imatinib	1	10
Second line (N=32)		
Imatinib dose increase	1	14
Sunitinib	2	11
Imatinib + sunitinib	2	1
Motesanib	2	1
Non-TKI therapy	1	5
Third line (N=16)		
Sunitinib after imatinib [b]	2	7
Sorafenib	3	3
Nilotinib	3	2
Imatinib after sunitinib	2	1
Imatinib + sirolimus	Unclear whether 1 or 2 [c]	1
Non-TKI therapy	Unclear whether 1 or 2 [c]	2

Source: Text in Cassier et al 2012.

[a] not reported separately for the *PDGFRA* D842V mutation subgroup

[b] ERG assumes this means second-line patients received increased-dose imatinib

[c] Not reported whether these patients had received sunitinib or increased-dose imatinib second line

Total number of TKIs	Number (%) of patients (N=58)
1	29 (50)
2	21 (36)
1 or 2 (unclear)	3 (5)
3	5 (9)

Appendix 2 Company and ERG assessments of study validity (questions 14-26 of the Downs and Black checklist)

The following table provides a comparison of the company's and ERG's assessments of the NAVIGATOR, BLU-285-1002 and Cassier studies for questions 14 to 26 of the Downs and Black checklist.[16] We encountered several problems whilst applying the checklist to the included studies, which are summarised below the table.

Question (as worded in the checklist and CS)	ERG interpretation (risk of bias: 'No'= high, 'Yes'=low) [a]	NAVIGATOR		BLU-285-1002		Cassier et al 2012	
		Company	ERG	Company	ERG	Company	ERG
14. Was an attempt made to blind study subjects to the intervention they have received?	'No' means lack of blinding could have introduced bias	No	Not applicable [b]	Not applicable	Not applicable [b]	No	Not applicable [b]
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	'No' means lack of blinding could have introduced bias	No	Not applicable [b]	Not applicable	Not applicable [b]	No	Not applicable [b]
16. If any of the results of the study were based on 'data dredging', was this made clear?	'No' means there were unplanned analyses which could have introduced bias	No	Yes [c]	No	Yes [d]	Yes	Yes [d]
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?	'No' means imbalances in follow-up were present which could have introduced bias	Yes	Yes [e]	No	Yes [e]	Yes	Yes [e]
18. Were the statistical tests used to assess the main outcomes appropriate?	'No' means inappropriate statistical tests could have introduced bias	Yes	Yes	Yes	Not applicable [f]	Yes	Not applicable [f]

19. Was compliance with the intervention(s) reliable?	'No' means compliance was inadequate, which could have introduced bias	Yes	Yes [g]	No	Yes [g]	No	Yes [g]
20. Were the main outcome measures used accurate (valid and reliable)?	'No' means there were problems with outcomes which could have introduced bias	Yes	Yes	Yes	Yes	Yes	Yes
21. Were the patients in different intervention groups (trials and cohort studies) recruited from the same population?	'No' means different intervention subgroups (e.g. dose, mutation) were not recruited from the same population, which could have introduced bias	No	Yes	No	Yes	Yes	Yes
22. Were study subjects in different intervention groups (trials and cohort studies) recruited over the same period of time?	'No' means different intervention subgroups (e.g. dose, mutation) were not recruited at the same time, which could have introduced bias	No	Yes	Yes	Yes	Yes	Yes
23. Were study subjects randomized to intervention groups?	This question is not applicable to single-group studies	Not applicable	Not applicable	Not applicable	Not applicable	No	Not applicable
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	This question is not applicable to single-group studies	Not applicable	Not applicable	Not applicable	Not applicable	No	Not applicable
25. Was there adequate adjustment for confounding in	'No' means variables other than the planned	No	Primary outcome	No	No [i]	Yes	No [i]

the analyses from which the main findings were drawn?	intervention could have explained the results		Yes; other outcomes not reported [h]				
26. Were losses of patients to follow-up considered?	'No' means there were missing data that were not accounted for which could have introduced bias	Yes	Yes [j]	Yes	Yes [j]	No	Yes [j]

[a] the company do not explain how they interpreted the questions and do not provide any explanations for their judgements
[b] single-group study in which blinding would not be feasible
[c] dose-group comparisons were pre-specified in the statistical analysis plan
[d] no evidence of unplanned analyses
[e] KM analysis of time-to-event outcomes captures variation in follow up duration
[f] descriptive analysis without formal statistical testing (statistical tests were employed in the Cassier study but for comparisons between different mutation subgroups which are not relevant to the current appraisal)
[g] compliance appears reflective of that likely in clinical practice
[h] possible explanatory variables were included in logistic regression on the primary outcome (ORR) (CS Table 8)
[i] no exploration reported of whether factors other than the intended intervention could have explained the observed outcomes
[j] all participants were accounted for when reporting outcomes

The following problems were encountered by the ERG when assessing the company's validity assessment using the Downs and Black checklist:

- The company have not explained how they interpreted the questions in the Downs and Black checklist in relation to the included studies. We have stated the ERG's interpretation in the table above to reduce subjectivity; however, it might be that the company's interpretation was different to ours.
- The company have not provided a rationale for their yes/no answers in the checklist. Some company answers appear inconsistent but it is not possible to be sure since no explanation is given.
- Overall, the validity questions of the Downs and Black checklist do not appear to be well-suited for assessing the NAVIGATOR, BLU-285-1002 and Cassier studies since many of the questions appear to be not applicable. The studies were single-arm (so randomisation and blinding questions are not applicable) and comparative analyses were only conducted for NAVIGATOR (against a historical control)

(so several statistical analysis questions are not applicable to the BLU-285-1002 and Cassier studies). The company have not explained why the Downs and Black checklist was selected given that other tools could also have been considered for evaluating non-randomised studies.[32]

- The company compared the total checklist scores for each study (based on 1 for each yes answer and zero for each no answer for all 26 questions) (CS Appendix D.3). However, we caution that total scores should be disregarded as they conflate reporting, bias and other aspects of "quality" based on an implausible assumption that the questions about different aspects of reporting and validity have equal weight.

As stated in section 3.2.2 above, the key ERG conclusions are that the included studies are inherently at risk of bias due to their single-arm designs and, in the case of the comparator studies, their retrospective designs.

Appendix 3 ERG checklist for clinical effectiveness searches

Checklist criteria	Details	ERG comments
CS section(s)	Appendix D.1 (B.2.1 gives no details; refers to the appendix)	Not applicable
Dates covered	Databases: no limit – 05/11/2019 Conferences: most recent two years available	Over 5 months old, hence updated by ERG
Reporting	Clear outline of database sources, except not clear which websites were searched (perhaps refers to the conference proceedings). Bibliographic database search strategies are presented in CS Appendix Tables 1-3. CS Appendix Table 4 summarises results (number of hits reported does not match the numbers in CS Appendix Tables 1-3, but a minor issue as the hits reported in the PRISMA diagram match those in CS Appendix Tables 1-3). The CS Appendix tables are clearly labelled with the bibliographic database and database host. Not reported which systematic reviews and meta-analyses were reference-checked.	No major concerns
Search strategy overall	Very sensitive strategy overall: extensive use of alternative search terms/drug synonyms, broader subject headings used, searched for comparators outside of the NICE scope, reference checking of other systematic reviews (stated but no details).	No concerns
Strategy PICO and terms	Several additional pharmacological comparators were searched for, not just those in the scope, The company did not search on any terms that would express BSC, meaning that searches may have missed studies on BSC alone.	The ERG searched Medline for BSC-only studies and found none that matched the scope (studies were identified but did not separate locally advanced from unresectable/metastatic GIST.
Strategy subject headings	None missing. Exploded broader heading for 'Gastrointestinal tumors', rather than using the specific heading for 'Gastrointestinal stromal tumors'. Relied on automatic mapping of subject headings for MeSH on PubMed.	No concerns

Strategy free-text terms	Comprehensive.	No concerns
Strategy syntax	All correct.	No concerns
Strategy structure	Boolean and combinations of lines/concepts all correct.	No concerns
Sources	Searched core databases: Medline, Embase, Medline-in-process, Cochrane library – CDSR and CENTRAL 3 x general cancer conference proceedings	ERG checked for any specific sarcoma cancer conference proceedings and checked a trial registry – Clinical Trials.gov – nothing further found.
Limits	Language limit (i.e. English only) was applied at screening stage instead of at search stage.	No concerns
Filters	Published search filters not used. The concepts for study types in the strategy are well defined and include correct and relevant terms. Case studies/reports, etc., were removed (using NOT) It is appropriate to search for other clinical studies in addition to RCTs for this disease population.	No concerns
Translation	Medline and Embase searched together within Embase.com. Assume automatic mapping of subject headings. The other searches carried out are consistent across the databases.	No concerns
Missing studies	None.	No concerns

Appendix 4 Overview of outcomes assessed in the NAVIGATOR study

Primary outcomes	Outcome definition	Data cut	Specified in Decision Problem	Used in Economic Model	ERG comments
Overall Response Rate	The proportion of patients with a confirmed best response of CR or PR, where either was confirmed at a subsequent assessment without intervening progression. Standard used: mRECIST Version 1.1	Nov 2018	Yes	No	Includes discussion of Clinical Benefit Rate (a secondary outcome below) and Disease Control Rate.
Disease Control Rate	The proportion of patients with a confirmed best response of complete response (CR), partial response (PR), or stable disease.	Nov 2018	No	No	Outcome defined in text of CS in relation to ORR.
Adverse events	Type, frequency, severity, timing and relationship to the study drug of any adverse events, serious adverse events, and changes in vital signs, electrocardiogram tests and safety laboratory tests.	Nov 2018	Yes	Yes	
Time on Treatment (CS section B.2.10, Adverse reactions)	Calculated as: (treatment end date – treatment start date +1)/7 (CS Tables 22 and 23). The treatment start date was the first dose date of study drug, and the treatment end date was the last dose date of study drug or data cut-off date, whichever was earlier. Treatment duration (weeks) was summarized using descriptive statistics. See CSR section 9.7.1.10.	Jan 2020	Yes	Yes	In decision problem, but not in NICE scope. Helps to interpret the adverse events.
Secondary outcomes					
Duration of Response	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. According to mRECIST 1.1. Sensitivity analysis was conducted using criteria in a study by Choi et al.	Nov 2018	Yes	No	Median DoR not reached for anticipated licensed dose. Not known to ERG if reached in Jan 2020 data cut.

Progression Free Survival	The time from the start of the treatment to the date of first documented disease progression or death due to any cause, whichever occurred first.	Jan 2020; Nov 2018	Yes	Yes	Time to event endpoints are difficult to interpret in non-randomised trials.
Clinical Benefit Rate	The proportion of patients with confirmed CR/PR/stable disease lasting four or more cycles from first dose date.	Nov 2018	No	No	See CS section B.2.6.3 – discussed as part of ORR.
Exploratory outcomes					
Overall Survival	The time from the start of treatment to the date of death. 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	Jan 2020; Nov 2018	Yes	Yes	Median survival not reached.
Time to Response	The time from the start of treatment to the time the response criteria for CR/PR were first met.	Nov 2018	No	No	Not in protocol, not in the decision problem, and not used in the economic model. Included in SAP as helpful to interpret study results. ERG agree.
Tumour reduction	Central radiology assessment. Sum diameter of target lesions change from baseline. According to mRECIST Version 1.1	Nov 2018	No	No	A clinical expert advisor to the ERG noted that HRQoL-related issues, e.g. pain, bloating and fatigue, improve markedly in response to tumour shrinkage.

					However, this outcome is not in the NICE scope nor in the company's decision problem.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Monday 6 July** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

ERG responses

Please note that page numbers referred to in the ERG's responses below refer to the version of the ERG report viewed with track changes (i.e. full markup).

Issue 1 Statements by the ERG imply that their base case is conservative

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.1; Page 87: The ERG states: 'We agree with the company's argument as in clinical practice it is generally observed that an effective treatment given in the early course of a disease leads to better survival outcomes'. The implication of this is that the ERG acknowledges that the overall survival Kaplan–Meier data from the NAVIGATOR trial represent an underestimate of the expected overall survival of the avapritinib population in practice. However, contrary to this, the treatment waning period was set to 1 month to visually align modelled overall survival to this Kaplan–Meier data. This line of interpretation is raised repeatedly throughout the document, for example in Section 3.2.1.3.	Based on the ERG's statement in Section 5.3.1, we propose that one or more of the following amendments are made: (i) the waning period is increased to more accurately reflect first-line patients; (ii) alternative justification of the 1-month waning period is provided, or (iii) an acknowledgement is added that the ERG base case is conservative (i.e. leading to an over-estimate of the incremental cost-effectiveness ratio [ICER]).	The ERG agrees with the company that NAVIGATOR most likely underestimates overall survival of patients receiving avapritinib in practice because 'better survival would be expected in clinical practice when avapritinib is used first line, rather than when used at a later line of treatment as in NAVIGATOR' (Page 87) and 'it is generally observed that an effective treatment given in the early course of a disease leads to better survival outcomes' (Page 87). However, the ERG's base case model assumptions are explicitly selected to give 'a close fit to the observed OS data' (Page 69). This suggests that the ERG's base case underestimates overall survival for avapritinib patients compared with what would be expected in practice. In addition to the reasons stated above, the ERG base case is likely to underestimate overall	Thank you for highlighting this. We have revised the text to clarify the ERG's view in section 5.3.1 on page 89 as follows: *We view that the company's argument may not be applicable for patients who have had a lot of prior TKIs as in the case of participants in the NAVIGATOR study where they received more frequent prior TKIs than would be expected in UK clinical practice. Therefore, we treat the modelled overestimation of OS with caution and explore this further in our scenario analyses in section 6.* With regard to treatment waning, our base case assumption of 1-month duration of treatment waning is based on expert

		survival in clinical practice, because: 1. As outlined in the company's response to clarification question B1, it is unlikely that any post-discontinuation treatment effect would be fully captured by the simple extrapolation of the full overall survival data, due to the short follow-up period (and the consequent incomplete time on treatment data). 2. Clinical advice received by the company indicated that the estimated overall survival of approximately 10 years for unresectable or metastatic *PDGFRA* D842V patients treated in first line with avapritinib would be reasonable. 3. The ERG's modelled overall survival extrapolation in Figure 5 is considerably below the Kaplan–Meier data from NAVIGATOR beyond 35 months, indicating that the ERG's base case also underestimates overall	clinical advice. To explore the impact of this assumption on the overall cost effectiveness results, we conducted a range of scenario analyses as below: - Varying the duration between 1 month and 4 years in the ERG corrected company's base case (Section 6.1 Table 33) - Varying the duration between 6 months and 2 years in the ERG preferred base case (Section 6.3 Table 36)

		survival relative to the NAVIGATOR data. Nevertheless, the waning period (the period over which a patient loses all treatment effect following treatment discontinuation) has been set to the minimum that the model will allow (1 month), resulting in estimates of [redacted] years below the expectations of clinical experts.	

Issue 2 Inclusion of untreated patients in the ECM arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4 and all subsequent sections: The ERG has set the first-line market share of imatinib to 20%, despite the fact that all first-line patients in the comparator data (BLU-285-1002 and Cassier) are treated with tyrosinase inhibitors (TKIs).	We propose that the ERG caveats the results concerning this aspect of the changes. It should be made clear that this assumes that outcomes would be the same for the 80% of patients that are not treated at baseline, and that this does not align with the clinical expectations in Table 27 of the ERG report.	There are several justifications for our proposed amendment: 1. These estimated market shares are not relevant to the population for which clinical evidence is available, as the comparator evidence is in a population that was treated with TKIs 2. If a subgroup of the population is not treated with TKIs, there is no evidence basis on which to assume that their baseline characteristics and outcomes	Not a factual inaccuracy. Advice from our clinical experts suggests that, in UK clinical practice, relatively few patients with the PDGFRA D842V mutation would receive TKI treatments due to their lack of efficacy and risk of toxicity. To reflect this, an assumption was made wherein 20% of the patients would receive imatinib, followed by 10% of patients receiving sunitinib and regorafenib, each

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		would be the same as the whole population (which an indirect treatment comparison [ITC] cannot account for, as there are no data for patients not treated with a TKI in BLU-285-1002). It may be expected that clinical outcomes would be better in patients treated with TKIs compared with untreated patients.	respectively, in the ECM arm. As pointed out in section 4.2.4 on page 67, we acknowledge that these estimates are uncertain, Nonetheless, we view that they provide a closer approximation of the likely estimates in UK clinical practice.

		3. In Table 27 the ERG shows that the clinicians consulted estimated considerably lower survival than the evidence used suggests. This difference in outcomes indicates misalignment between the population for which there is clinical evidence, and the population for which the clinical experts were providing estimations, both in terms of proportions of patients receiving treatment and clinical outcomes 4. In the NAVIGATOR trial, most patients [redacted] were previously treated with TKIs, contrary to the ERGs argument that only a minority of patients would receive these treatments. Although the NAVIGATOR trial was not designed to estimate the proportion of patients treated with a TKI, these proportions show that the ERG expectation may represent a under-estimate. 100% of the patients in the BLU-285-1002 trial were treated with TKIs	

Issue 3 Clarification of treatment patterns in UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.3.1; Page 19: The ERG states: 'Among those patients who do receive imatinib, very few, if any, would subsequently receive sunitinib or regorafenib, due to lack of effectiveness and risk of toxicity'.	We suggest that the ERG amends or softens this statement, as it does not align with the evidence provided by clinical experts surveyed by the company, nor the evidence from the NAVIGATOR study, where the majority of the UK patients included received prior treatment with TKIs within standard clinical practice.	This statement does not align with the evidence provided and does not reflect the uncertainty in UK clinical practice for these patients.	Not a factual inaccuracy. The difference between the company studies and expected UK clinical practice, as well as heterogeneity among expert opinions are precisely the points we are making in the ERG report.
Section 2.2.3.1; Page 19: The ERG states: 'Patients with the PDGFRA D842V mutation in UK clinical practice would predominantly receive BSC, with relatively few receiving imatinib and very few if any would go on to receive sunitinib or regorafenib. However, the clinical experts acknowledged that there is likely to be considerable variation in practice'.	We suggest that the ERG softens this statement, as it is difficult to make such firm conclusions given the conflicting evidence provided by clinical experts consulted by the company and the ERG, and the acknowledged variation in clinical practice.	Given the acknowledgement from clinical experts that there is likely to be considerable variation in practice, the limited size of the patient population, and the clinical input received by the company, it does not seem reasonable to conclude that few patients would receive imatinib and very few if any would go on to receive sunitinib or regorafenib. Any patients receiving these treatments would make up a reasonable proportion of the population, given the small size of the overall population.	Not a factual inaccuracy. We are correctly reporting the opinions of our clinical expert advisors. We explicitly state that there is likely to be considerable variation in clinical practice.

Section 3.2.1.3; Page 35: The ERG states: 'The CS does not explain why patients with the PDGFRA D842V mutation in the NAVIGATOR study received prior TKIs'.	We suggest that this statement is removed.	Before study entry, patients were treated as per clinical practice. It would be unusual for a study to discuss rationale for patient treatment before entering a study, as this is outside of the control of the study investigators.	Not a factual inaccuracy. The CS states that patients with the PDGFRA D842V mutation are resistant to existing TKIs and do not respond to these therapies (CS section B.1.3.1). Therefore, it is of interest and important for this technology appraisal, to understand why patients with the mutation received TKI therapy.
Section 3.2.1.3; Page 36: The ERG states: 'The rationale for why patients with the PDGFRA D842V mutation group in these studies received TKIs is not discussed'. Statement is repeated on Page 65	We suggest that this statement is removed.	In Section B.1.3.3 of the CS, it is explained that these TKIs are all approved for use in patients with unresectable or metastatic disease, regardless of mutation status. In Section B.1.3.2.2 of the CS, we state: 'Therefore, in the absence of any other effective therapy option, and in line with NICE-approved treatment options, clinical experts from England and Wales stated that they would always inform their patients that the available TKIs have a very low probability of being effective for patients with their mutational status, and that they may experience adverse	Not a factual inaccuracy. The ERG statements on pages 35 and 36 refer to the NAVIGATOR study. The opinions of clinicians in England and Wales reported in the CS refer to a different population.

		effects, but still give them the option of receiving treatment as per standard practice'.	
Section 3.2.1.3; Page 36: The ERG states: 'The CS does not explicitly state whether any TKIs in the NAVIGATOR study were employed in the adjuvant setting (i.e. prior to unresectable or metastatic disease diagnosis)'.	We suggest that this is clarified to confirm that this is related to TKI use before the NAVIGATOR study, rather than TKI use within the NAVIGATOR study.	As written, the statement by the ERG is incorrect, as the NAVIGATOR study was conducted in patients with unresectable or metastatic GIST and was a single-arm study of avapritinib; therefore, no other TKI use in the trial was employed and no treatment was in the adjuvant setting.	Thank you for highlighting this inaccuracy. We have amended the text on page 36 to clarify that we are referring to prior TKI therapy.

Issue 4 Health-state utility values from VOYAGER

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In multiple places throughout the ERG report (Section 4.2.7, Section 5.3.4 [Table 32], Section 6.1 [Table 33], Section 6.2), the ERG suggests that the VOYAGER health state utilities are useful and appropriate (note that these were not yet available at the original company submission [CS] to NICE), yet do not	We suggest that the ERG either: 1) update their base case including the utilities from VOYAGER, or 2) caveats their base case by stating that it is not using the most up to date and appropriate health state utility values. Perhaps: 'The ERG base case is conservative, as it does not include the most appropriate health state utilities for the later stages of	The statement that these are appropriate and the use in the base case should be mutually inclusive, otherwise they are a logical contradiction.	To clarify the ERG's position regarding using the utilities from VOYAGER as a scenario analysis, we have added the following ERG conclusion in section 4.2.7.3, page 79). ***ERG conclusion***

include them in their preferred set of assumptions.	the disease, which decrease the ICER associated with avapritinib due to its positive incremental expected time in all health states.'		*Whilst the VOYAGER data are relevant (as the only study that provides HRQoL data directly for avapritinib), they are based on a very small sample size for the PGDFRA D842V mutation subgroup. Therefore, we consider it appropriate to include the utility data obtained from this study in a scenario analysis (as shown in section* ***Error! Reference source not found.****) rather than in our preferred base case.*

Issue 5 Justification for inclusion of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1; Page 11: The ERG states: 'these results are subject to considerable uncertainty due to immaturity of the survival outcomes data (median OS was not reached), small sample sizes, inherent	We suggest adding a caveat that, due to the limitations with the available evidence, this remains the best possible source of comparator evidence.	This provides needed context for this critique, and a justification for why this evidence was included.	Not a factual inaccuracy. However, we are happy to clarify that these are currently the best OS and PFS data available for this technology appraisal. We have added a sentence at

risks of bias, limitations in the company's studies, and limitations in the ITC methodology'.			the end of the second paragraph on page 11 stating this.

Issue 6 Expected CHMP date is incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 17, the ERG states that the expected Committee for Medicinal Products for Human Use (CHMP) positive opinion is due in [redacted]. Due to exogenous factors, this is now [redacted].	The statement should be amended to: [redacted]	This information is now out of date.	Not a factual inaccuracy at the time of writing. However, we have updated the date on page 17 as requested.

Issue 7 Prognostic factors included in ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2; Page 12 Section 3.5.2; Page 52 Section 3.5.6; Page 58 Section 3.6; Table 15; Page 59 The ERG queried the lack of inclusion of 'type of prior TKI' and tumour size in the ITC. It is unclear to us what is meant by 'type of TKI', although our interpretation is that this refers to grouping patients based on which prior TKI(s) they had received. The use of either of these as prognostic factors in the ITC was not feasible.	We suggest that the ERG is clear in each instance if they are referring to the specific TKIs used, and add that tumour size in BLU-285-1002 was only available at diagnosis and not at first treatment for unresectable or metastatic disease, as is the population of interest for this CS.	Tumour size was only measured at the time of diagnosis and was not available at the timepoint at which the analysis was conducted (initiation of treatment with first TKI). As the time between diagnosis and initiation of the first TKI varied between patients, including this variable in the ITC would have introduced bias. The CS explains that variables in the ITC were used at first treatment for unresectable or metastatic disease, as this is the population of interest for this CS. Using specific TKI(s) received as a prognostic factor was not feasible due to the small sample size.	Thank you for this clarification and for highlighting that "type of TKI" is ambiguous. We have corrected this ambiguity and amended the text as suggested on page 52. We have also amended the bullets on page 58, Table 15 on page 59, and the Executive Summary on page 12 to clarify that specific prior TKIs and tumour size (as well as performance status score) could not be included as covariates in the analysis due to data limitations.

Issue 8 Clinical expert statement does not apply to the relevant population for the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.1; Page 17: The ERG states: 'although a clinical expert advising the ERG noted that patients with the PDGFRA D842V mutation generally have a more indolent disease course than patients with KIT exon 11 mutations'.	We propose that this statement is removed or clarified to note that this statement applies for *PDGFRA* D842V patients earlier in their disease course. Once patients have advanced to unresectable or metastatic disease, which is the population of interest for this appraisal, this statement no longer applies and *PDGFRA* D842V patients have a worse prognosis than those without the mutation, due to the lack of an effective treatment option.	The statement, as presented in the ERG report, is misleading in how it applies to the population of interest for this CS.	Thank you for highlighting the potential for this statement on page 17 to be misinterpreted. In the interests of clarity and accuracy we have removed this statement.

Issue 9 Guidelines for *PDGFRA D842V* mutation patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.3.1; Page 18: The ERG states: 'neither the NICE guidance, nor the clinical guidelines provide recommendations for treating unresectable or metastatic GIST in patients with the PDGFRA D842V mutation'.	We suggest that this is amended to: 'while the NICE guidance does not provide specific recommendations for treating unresectable or metastatic GIST in patients with the *PDGFRA* D842V mutation, these patients are also not excluded from the current guidance, which	This change provides additional clarity and avoids potential misunderstanding of why TKIs may be considered for use in patients with the *PDGFRA* D842V mutation.	Not a factual inaccuracy. We believe this suggested change would reduce clarity, since clearly the population referred to in the NICE guidance is not the population in the current decision problem.

	applies to all patients with unresectable or metastatic GIST.'		

Issue 10 Correction of company clinical survey results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.3.1; Page 19: The ERG states: 'in the company's clinician survey only two out of five clinicians responded that they would treat these patients with TKIs'. While the question was put to five clinicians, one of the respondents indicated that patients would be referred to clinical trials or compassionate use programmes as opposed to receiving imatinib, sunitinib and regorafenib. However, the question text asked respondents to exclude these patients from their consideration. Therefore, this response was considered invalid and excluded, resulting in an agreement rate of 50% of clinicians (two out of four).	We propose that the ERG's statement is clarified to read: 'in the company's clinician survey two out of four clinicians responded that they would treat these patients with TKIs'.	The original statement does not accurately reflect the survey results.	Not a factual inaccuracy. The expert in question has clearly stated that patients would be referred to clinical trials or compassionate use programmes as opposed to receiving imatinib, sunitinib and regorafenib. Excluding clinical trials and compassionate use programmes from the survey question misrepresents the options available in clinical practice. We therefore believe this survey question is misleading.

Section 4.2.7.2; Page 76: The ERG states: 'We note that this set of utilities was assessed by five clinical experts advising the company, who were uncertain about the utility for progressive disease'. It is not the case that the surveyed clinicians were uncertain about the utility for progressive disease. As stated in Section B.3.4.5 of the CS, '5/5 (100%) clinicians agreed that the utility values shown in Table 50 are likely to be reflective of the HRQL of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in current UK clinical practice. Furthermore, 5/5 (100%) agreed that these utility values were also likely to be reflective of patients in UK clinical practice following the introduction of avapritinib, excluding modifying factors such as AEs.'	We propose that the ERG's statement is removed and replaced with: 'this set of utilities was assessed by five clinical experts advising the company. All of these clinicians agreed that these utility values are likely to be reflective of the health-related quality of life (HRQL) of patients with unresectable or metastatic *PDGFRA* D842V-mutated GIST in current UK clinical practice, and that are also likely to be reflective of patients in UK clinical practice following the introduction of avapritinib, excluding modifying factors such as AEs.'	This is factually inaccurate.	Thank you for the clarification. We have revised the text in section 4.2.7.2; Page 77 as follows: *We note that this set of utilities was assessed by five clinical experts advising the company, who reportedly agreed these values to be reflective of patients with unresectable or metastatic GIST in UK clinical practice. To assess the impact of utilities on the overall cost effectiveness results, the company also conducted a scenario analysis using an alternative progressive disease utility value, from TA86/20911,39 and TA17912 (CS Table 64). The ICER increased less than £1,000 for this analysis.*

Issue 11 Correction of BLU-285-1002 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.1.2; Table 5; Page 33: The heading for BLU-285-1002 reads: 'Participants whose first TKI was for unresectable or metastatic disease'.	We suggest correcting to: 'Participants receiving their first TKI for unresectable or metastatic disease'.	The statement is incorrect as it currently reads, as the data were selected from the point at which patients received their first TKI to treat unresectable or metastatic disease, which would not necessarily have been their first TKI.	Thank you for highlighting the possibility of ambiguous interpretation here. We have amended the column heading in Table 5 (page 33) as suggested.

Issue 12 Censoring methods for PFS in the NAVIGATOR study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.4; Page 41: The ERG states: 'The censoring method used for the PFS outcome (EMA or FDA censoring rules) is not fully clear, however'.	This can be amended to state that the EMA censoring rule was used for the PFS outcome.	This is a simple clarification that the company is happy to provide.	Not a factual inaccuracy. But thank you for the clarification. We have updated the text on page 41 to reflect this.

Issue 13 Presentation of evidence for the BLU-285-1002 study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.5; Page 41: The ERG states: 'Relatively limited data from BLU-285-1002 are reported in the CS'.	We suggest that this statement is removed.	The statement is incorrect. Data for the BLU-285-1002 study, including detailed results by line of treatment, are presented in Appendix D.1, Table 14 (Page 34), Table 16 (Page 37) and Table 17 (Page 38).	Thank you for highlighting this. We have removed the statement on page 41 as suggested, and inserted a cross-reference to Appendix D Tables 14, 16 and 17.

Issue 14 Justification for ERG selection of evidence from the BLU-285-1002 study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.5.1, Table 6, Page 42 Section 3.2.5.3, Table 8, Page 43 Section 3.2.5.3, Table 9, Page 44 The ERG presents data for the BLU-285-1002 study only for patients treated at second-line. In our opinion, it would be more appropriate to present the data for the full study population in these tables.	We suggest that the ERG should add justification for why the data used by the ERG have been selected, or further detail should be provided for completeness. Detailed results for the BLU-285-1002 study by line of treatment, are presented in Appendix D.1, Table 16 (Page 37) and Table 17 (Page 38) of the CS.	It is unclear why data for patients treated at second-line have been selectively presented.	Thank you for highlighting this. We misinterpreted the second-line N=19 column in the CS tables as reflecting the full cohort with unresectable or metastatic disease. We have corrected this by including all available data for second- and third-line patients in BLU-285-1002 in ERG Tables 6, 8 and 9 and we have updated the text that references these tables accordingly (pages 42, 43, 44). These data show that PFS was longer in 3rd-line than second-line patients, albeit with small sample sizes and high uncertainty, and we have added a sentence on page 44 noting this.

Issue 15 NICE DSU TSD14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

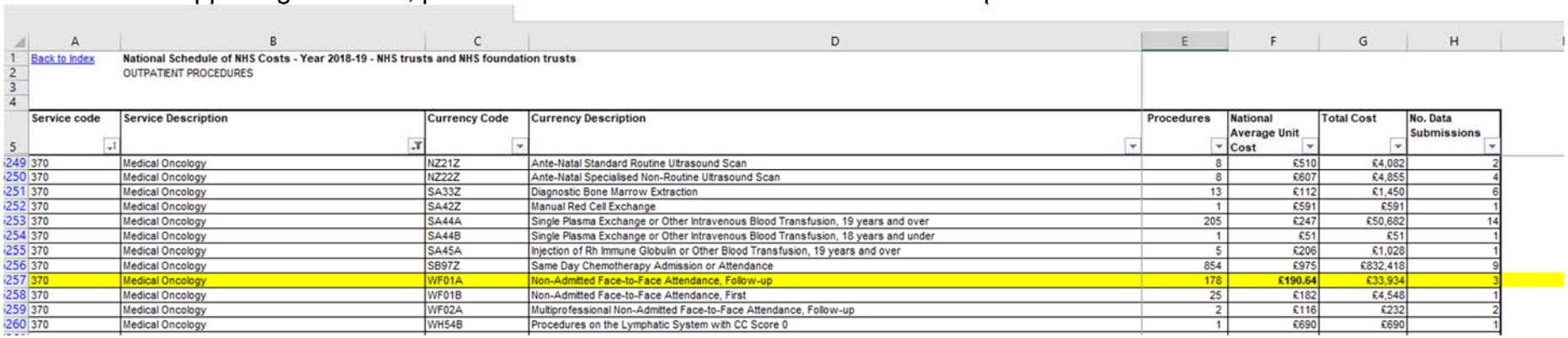
Section 1.3; Page 13 Section 4.2.6.1; Page 69 Section 5.3.4, Table 32; Page 93-95 Section 6.2; Page 98 It is stated that NICE DSU TSD 14 recommends that the same survival distribution should be used across arms. The ERG also suggests that this should be the case across different treatment lines. This does not accurately reflect the full guidance provided in TSD 14.	We propose that statements suggesting that the same curve should always be used across arms are softened to align with TSD 14. As a suggestion: 'NICE TSD 14 advises that use of the same distribution across arms is often reasonable, but that distributions should be considered independently according to clinical input and differences in the shape of the underlying hazard (for example if the hazards are not parallel).' Furthermore, we propose that the statement suggesting that the same distribution of survival should apply at subsequent lines of therapy should be removed, as this is not accurate.	NICE DSU TSD 14 states that it is 'reasonable' to use the same distribution of survival across arms. However, the document goes on to state that use of different distributions is permissible. It is therefore not the case that the same curve should always be used. Furthermore, outcomes in one line are not indicative of the survival distribution in a subsequent line, so this should not be used as a basis for selection.	Not a factual inaccuracy. But thank you for highlighting the possibility of misinterpretation. For clarity, we have revised the text as follows: Section 1.3, page 14: *To align with recommendations in NICE DSU TSD 14, we view it appropriate to use the same survival model for both the treatment arms.* Section 4.2.6.1, page 70: *Firstly, NICE DSU guidance 14 states that the same distribution would be appropriate for both treatment arms.* Text in Table 32, page 96: *To align with the NICE DSU methods guide, both treatment arms should preferably use the same*

			distribution (see section 4.2.6). A minor typographical error has been corrected in section 6.2 (within point 4), page 100. With respect to model fit for PFS of subsequent lines of treatment, we preferred the Weibull distribution as this model provided a better statistical fit (as pointed out in section 4.2.6.4).

Issue 16 Cost of outpatient care visits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.8.2; Page 82 Section 5.3.3; Table 29 The ERG provides a correction to a resource cost for outpatient visits from £190.64 (original value) to £194.17 (ERG value). However, we believe that the source value originally used is correct. For transparency, a screenshot of the value in question is shown below.	If the ERG agrees that the original source value is correct, we suggest that the cost is reverted to the originally value, all reference to this as an error are removed and the results updated.	The ERG states the cost of an outpatient care visit in NHS reference costs was £194.17 (rather than £190.64 used in the CS and company model). However, £190.64 is correct based on NHS reference costs 2018/19, OUTPATIENT PROCEDURES tab, currency code WF01A, service description medical oncology (service code 370). The source of the £194.17 value is unclear to us.	Not a factual inaccuracy. We view that the appropriate costs for an outpatient visits is £194.17. The value is derived from NHS reference costs 2018/19, CL tab, currency code WF01A, service code 370, service description: Medical Oncology). For clarity, we have added the following text in section 4.2.8.2, page 83: *The ERG note that the cost for an outpatient care visit in NHS reference costs was £194.17 rather than £190.64 as used in the CS and company model. We obtained this value from NHS reference costs 2018/19, CL tab, currency code WF01A, service code 370, service description: Medical Oncology.*

As additional supporting evidence, please find below a screenshot of the value in question:



	A	B	C	D	E	F	G	H
1	Back to Index	National Schedule of NHS Costs - Year 2018-19 - NHS trusts and NHS foundation trusts						
2		OUTPATIENT PROCEDURES						
3								
4								
5	Service code	Service Description	Currency Code	Currency Description	Procedures	National Average Unit Cost	Total Cost	No. Data Submissions
249	370	Medical Oncology	NZ21Z	Ante-Natal Standard Routine Ultrasound Scan	8	£510	£4,082	2
250	370	Medical Oncology	NZ22Z	Ante-Natal Specialised Non-Routine Ultrasound Scan	8	£607	£4,855	4
251	370	Medical Oncology	SA33Z	Diagnostic Bone Marrow Extraction	13	£112	£1,450	6
252	370	Medical Oncology	SA42Z	Manual Red Cell Exchange	1	£591	£591	1
253	370	Medical Oncology	SA44A	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	205	£247	£50,682	14
254	370	Medical Oncology	SA44B	Single Plasma Exchange or Other Intravenous Blood Transfusion, 18 years and under	1	£51	£51	1
255	370	Medical Oncology	SA45A	Injection of Rh Immune Globulin or Other Blood Transfusion, 19 years and over	5	£206	£1,028	1
256	370	Medical Oncology	SB97Z	Same Day Chemotherapy Admission or Attendance	854	£975	£832,418	9
257	370	Medical Oncology	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	178	**£190.64**	£33,934	3
258	370	Medical Oncology	WF01B	Non-Admitted Face-to-Face Attendance, First	25	£182	£4,548	1
259	370	Medical Oncology	WF02A	Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	2	£116	£232	2
260	370	Medical Oncology	WH54B	Procedures on the Lymphatic System with CC Score 0	1	£690	£690	1

Issue 17 Comparison to previous HTAs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.1; Page 88: The ERG states: 'The company conducted appropriate internal validity and face validity checks. However, they did not provide any comparison of the model results in the current appraisal against those from previous Technology Appraisals'.	We propose that the second sentence is revised to reflect the fact that no health technology assessments (HTAs) have been conducted in the specific population of interest (unresectable or metastatic *PDGFRA* D842V-mutated GIST), and therefore that a comparison would not be possible. For example: 'The company conducted appropriate internal validity and face validity checks. The company did not provide any	The criticism is unjustified, as there are no other HTAs in D842V GIST.	Not a factual inaccuracy. However, for clarity we have revised the text in the ERG conclusion within section 5.3.1, page 90 as follows: *The company conducted appropriate internal validity and face validity checks. Whilst there are no previous technology appraisals in the*

	comparison of the model results in the current appraisal against those from previous technology appraisals due to the absence of previous HTAs in this indication'		*GIST population with a PDGFRA D842V mutation, we view it reasonable to compare the model results in the current appraisal against 3 previous appraisals in GIST (including an update) i.e. TA86/TA209; TA179 and TA488) to provide some means of cross-validation.*

Issue 18 Contradiction on replicating the PSA following clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.3; Page 85 Section 5.3.3, Table 29; Page 90 The ERG states in Section 5.3.3 that they were able to replicate the probabilistic sensitivity analysis (PSA), yet state in Section 5.2.3 that they were unable to replicate it.	We suggest that this inconsistency should be addressed.	Inconsistency.	Not a factual inaccuracy. The ERG statement in section 5.2.3, Page 87 is in relation to the company's original model whilst our statement in section 5.3.3, Table 29 pages 92-93relates to the revised version of the company model that was submitted as response to company's clarification question B4. For clarity, we have added a sentence in section 5.2.3 page 87 as follows: *The ERG were able to replicate the PSA in this updated version of the model.*

Issue 19 The use of the Downs and Black checklist for quality appraisal

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.1; Table 3; Page 27: The ERG states that it was unclear that the risk of bias assessment (or other study assessment) was conducted by two or more reviewers independently.	We suggest that this is changed to reflect that the risk of bias assessment was conducted alongside the data extraction by two independent reviewers.	The risk of bias assessment for all the studies included in the review was conducted alongside the data extraction. Hence, each of the two reviewers who performed data extractions also conducted the risk of bias assessment independently. Data extraction was performed by one researcher and verified against the original source by a second researcher. The risk of bias assessment also followed the same pattern.	Not a factual inaccuracy as this s not reported in the CS. However, as this information has now been provided, we have updated Table 3.
Appendix 2; Page 113–114: The ERG states: 'Overall, the validity questions of the Downs and Black checklist do not appear to be well-suited for assessing the NAVIGATOR, BLU-285-1002 and Cassier studies since many of the questions appear to be not applicable. The studies were single-arm (so randomisation and blinding questions are not applicable) and comparative	We suggest that the question on the validity of the Downs and Black checklist is removed, as they are recommended for use by the Cochrane Centre for Reviews and Dissemination (CRD).	As per the CRD's guidance for undertaking reviews in health care, the below text has been reported on Page 43, which states that for complex projects that include multiple types of study designs, we can use a single checklist like Downs and Black. 'In general checklists tend to be specific to particular study designs, and where reviews include more than one type of	Not a factual inaccuracy. The ERG's concerns about the risk of bias assessment are explicitly stated in Appendix 2 and are independent of any guidance issued by other organisations (CRD's guidance relates more generally to "quality" rather than specifically to systematic error and the Downs and Black checklist

analyses were only conducted for NAVIGATOR (against a historical control) (so several statistical analysis questions are not applicable to the BLU-285-1002 and Cassier studies). The company have not explained why the Downs and Black checklist was selected given that other tools could also have been considered for evaluating non-randomised studies'.		study design, separate lists can be used or a combined list selected or developed. Checklists have also been developed for use with both randomised and non-randomised studies such as that by Downs and Black.' In addition, the Downs and Black checklist has been used widely and successfully across several NICE submissions and has been widely accepted as a powerful tool for conduction risk of bias assessment.	is referred to by CRD only in a general sense). We are unaware of "widespread and successful" use of the Downs and Black checklist in NICE submissions (the key point is whether a tool is fit for purpose and used appropriately rather than whether it is used widely).

Issue 20 Numerical errors/inconsistencies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.5.4; Page 44: The ERG states: 'Median PFS was [redacted] months at the latest (January 2020) data cut compared with only [redacted] months in the ECM studies'.	Please correct to: 'Median PFS was [redacted] months at the latest (January 2020) data cut compared with only [redacted] months in the ECM studies'.	Rounding is not consistent with the rest of the reporting of the results and is biased towards ECM.	Thank you for alerting us to this discrepancy. We have updated the % values on page 44 accordingly.

Section 3.3.1; Page 46: The ERG states: 'Overall, [redacted] % of patients died within 30 days of receiving avapritinib'.	Please correct to: 'Overall [redacted]% of patients died within 30 days of their last dose of avapritinib'.	The statement by the ERG may be misleading and could be interpreted as patients died within 30 days of starting avapritinib, which is incorrect.	We agree there is potential for misinterpretation and have made the suggested amendment on page 46.

Issue 21 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.1; Page 17: The ERG states: 'GISTs are rare. They account for 01.-3.0% of all gastrointestinal malignancies'.	Correct to: '0.1–3.0%'	Correction of typographical error	Thank you for alerting us to this. We have made the correction (page 17)
Section 3.2.1.1; Page 30: The ERG states: 'However, in BLU-285-2001 most patients had initially received adjuvant TKI therapy for locally advanced GIST…'	Correct to 'BLU-285-1002'	Correction of typographical error	Ditto (page 30)
Section 3.2.5.3; Page 43: The ERG states: 'median OS in the BLU-285-1002 and Cassier studies was [redacted] % and 14.7% respectively'.	Please correct to: 'median OS in the BLU-285-1002 and Cassier studies was [redacted] months and 14.7 months, respectively'.	Correction of typographical error	Ditto (page 43)
Section 3.3.1; Page 46: The ERG states: 'Overall, [redacted] % of all patients in NAVIGATOR who received avapritib (N=237)'.	Correct to: 'who received avapritinib'	Correction of typographical error	Ditto (page 46)
Section 3.4.3; Page 49: The ERG states 'This is discussed in section 3.4.2 below'.	Please correct to: 'This is discussed in section 3.5.2 below'.	Correction of typographical error	Ditto (page 49)

Issue 22 AiC/CiC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.1; Page 29: The ERG states: 'The company advised in clarification response A1 that the final CSR for NAVIGATOR will not be available until [redacted]'. The date of availability of the final NAVIGATOR clinical study report (CSR) is commercial in confidence.	Please mark as commercial in confidence as shown	This information is commercially sensitive	Thank you for alerting us to this. We have updated the confidential mark-up (page 29)
Section 3.2.5.3; Page 43: The ERG states: 'the CS notes that [redacted] of the [redacted] UK patients in the study were still alive at the time of the January 2020 data cut'. However, the number of patients still alive is not marked as commercial in confidence.	Please mark as commercial in confidence as shown	This information is commercially sensitive	Ditto (page 44)
Section 5.3.1; Page 86: The ERG states: 'This scenario increased the ICER for avapritinib versus ECM by approximately [redacted] compared to the company's base case ICER'. The difference in the ICER is not marked as commercial in confidence.	Please mark as commercial in confidence as shown	This information is commercially sensitive	Ditto (page 86)

Section 5.3.1; Page 88: Figure 7 should be marked as commercial in confidence.	Please mark Figure 7 as commercial in confidence	This information is commercially sensitive	Ditto (Figure 7 has been marked with a blue border to indicate CIC)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
1. Treatment pathway in economic model	**The company** base case economic model for the PDGFRA D842V-mutated GIST treatment pathway is set out as below: • Intervention arm: Avapritinib (1st line), Standard of Care (SoC) at 2nd line and SoC at 3rd line • Comparator arm: ECM which comprises of imatinib (1st line), sunitinib (2nd line) and regorafenib (3rd line) [See p.84 to 86 company submission] **The ERG** stated that there is uncertainty in the clinical treatment pathway, regarding the proportions of PDGFRA D842V patients who would receive imatinib, sunitinib, regorafenib and/or best supportive care (BSC). In the company's clinical studies, the majority of patients received prior tyrosine kinase inhibitors (TKIs) whereas in UK clinical practice it would be expected that most patients would receive BSC (see p.18 & 19 and p.35 ERG report). It highlighted that patients in the economic model are assumed to have had no previous TKIs unlike those in the NAVIGATOR and BLU-285-1002 studies (see issue 2). This means that there is uncertainty around the appropriateness of the modelled patient population (see sections p.65 & 66 ERG report). Clinical experts advising the ERG agreed that few patients would receive TKIs in clinical practice. They estimated 20% of patients would receive imatinib and fewer than 10% of patients would receive sunitinb and regorafenib, although these estimates are uncertain (see p.66 ERG report). The ERG base-case assumption for proportion of patients receiving TKIs in established clinical	**The technical team agree that there is uncertainty regarding the treatment pathway used in the company's economic model.** **The technical team would like clinical expert input on which treatments would be used 1st, 2nd and 3rd line in established clinical management. We would also like clinical expert input on the the proportions of patients receiving 1st, 2nd and 3rd line established clinical management to explore if the ERG's approach more accurately reflects the treatment pathway for people with PDGFRA D842V GIST in England.**

	management is 20% imatinib, 10% sunitinib, 10% regorafenib (see p.14 ERG report).	
2. Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs	**The company** clinical studies, NAVIGATOR and BLU-285-1002 allowed patients to receive TKIs prior to treatment with avapritinib or established clinical management (ECM). The company clinical experts stated that the population seen in the NAVIGATOR study was reflective of the unresectable or metastatic PDGFRA D842V-mutated GIST population that they would see in clinical practice in England and Wales (see p.32 company submission) **The ERG** noted that the participants in the NAVIGATOR study (recieving avapritinib) received more frequent prior TKI use than would be expected in UK clinical practice, despite TKIs being ineffective in the PDGFRA D842V subgroup. The TKI use in the BLU-285-1002 study (receiving ECM) is unclear as it was not reported for the relevant subgroup of patients who had unresectable/metastatic GIST and the PDGFRA D842V mutation (see p.36 ERG report).	**There is uncertainty that the population in the clinical trials is generalisable to the NHS because many participants received prior TKI therapy which does not reflect clinical practice in England.** **The technical team would like clinical input on the generalisability of this population to that seen in the NHS in England. We would also like clinical expert input on whether the treatment effect would be similar in people who have recieved prior therapy with TKIs to those who have not.**
3. Modelling time on treatment	**The company** stated that time on treatment (ToT) for avapritinib was captured and extrapolated using a Gompertz parametric model because this provided clinically plausible results based on the inverse probability weighted (IPW) data from the NAVIGATOR study, using the 17 January 2020 data cut (see p.111 to 114). **The ERG** disagreed with the choice of the Gompertz distribution for ToT for avapritinib. The ERG prefer the Weibull model for the ECM arm of 2nd line and 3rd line treatments because it is consistent with the model used for PFS and provides a better statistical fit to the observed data (see p.72 ERG report). The ERG base-case assumes ToT	**The technical team agree with the ERG that the Weibull distribution curve should be applied for ToT because it is consistent with the technical teams preferred model used for PFS (see issue 5) and provides a better statistical fit to the observed data.**

	for avapritinib to be equal to PFS. The ERG stated that the modelled outcomes do not provide a close fit to the observed ToT Kaplan-Meier data for avapritinib. In addition, there are further inconsistencies in modelling ToT for the dose intensity of the comparator treatments. These issues produce a significant underestimate of the treatment cost for avapritinib (see p.13 & 73 ERG report).	
4. Extrapolation of overall survival	**The company** stated that overall survival (OS) in the avapritinib arm was captured and extrapolated based on the information available from the NAVIGATOR trial, as of 17 January 2020. The OS analysis from NAVIGATOR used censors for discontinuation events and so captures mortality only for those patients still receiving avapritinib (see p.92 company submission). The company used a log-normal model in the base case to extrapolate OS for people receiving avapritinib with clinical input suggesting that the final OS estimates were clinically plausible. A Weibull parametric curve is used in the base case model for ECM because it has the best statistical fit as well as good visual fit to the observed data in the IPW analysis of the BLU-285-1002 study (see p.96 company submission) **The ERG** state that fitting OS to the uncensored Kaplan-Meier data is preferable (see p.68 ERG report). The ERG has continued to use the company model in the ERG base case, but corrected the OS extrapolation by varying the treatment waning duration (see issue 6). **The ERG** highlighted that NICE DSU guidance 14 states that the same distribution would be appropriate for both treatment arms. So, a Weibull distribution should be used	**There is uncertainty in the choice of distribution model to extrapolate overall survival. The technical team would like the company to explore conventional approaches to extrapolation using the OS data from the NAVIGATOR study, rather than the components of pre-discontinuation mortality, time on treatment and ECM survival from the BLU-285-1002 study. This should be considered alongside the treatment waning approach (see issue 6).** **The technical team would like clinical input on which extrapolation model gives the most clinically plausible estimates for overall survival.**

	for both avapritinib and ECM. It noted that changing the distribution from log-normal to Weibull has a minimal effect on the cost effectiveness results (see p.69 ERG report).	
5. Extrapolation of progression-free survival for 2nd and 3rd line ECM treatments	**The company** used data from the NAVIGATOR study to capture progression-free survival (PFS) for the avapritinib arm of the base-case economic model and the IPW BLU-285-1002 study data for the sequence of treatments in the ECM arm (see p.100 & 111 company submission). Extrapolated PFS (censored for death) for each line of therapy was done using the following distribution curves: • 1st line: Avapritinib = Weibull, ECM (imatinib) = Weibull • 2nd line (sunitinib): Log-logistic • 3rd line (regorafenib): Gompertz **The ERG** agree with the company in using the Weibull distribution curve for extrapolating PFS for avapritinib and 1st line ECM (imatinib) because there is a reasonable fit to the observed data (see p.70 & 71 ERG report). For 2nd line ECM (sunitinib) and 3rd line ECM (regorafenib) the ERG disagree with the company choice (log-logistic and Gompertz distributions respectively) and suggest that the Weibull would be a better distribution curve to use because it is consistent with the 1st line model and provides a better statistical fit (see p.71 & 72 ERG report)	**The technical team agree that the Weibull distribution curve should be applied to extrapolate PFS for 2nd and 3rd line treatments because it is consistent with the 1st line model and provides a better statistical fit.**
6. Treatment waning effect	**The company's** base case model used a log-normal distribution for overall survival (OS) survival and assumes a gradual movement of OS hazard from the avapritinib arm to the established clinical management (ECM) arm after stopping treatment with avapritinib. This means a gradual loss of treatment effect over a period of 5 years (60 months). It states that clinical experts support both the use	**The technical team considers that a treatment effect of 5 years may be overly optimistic, but acknowledge that this remains uncertain.**

	of a log-normal distribution and treatment waning effect assumption (see p.91 & 92 company submission). **The ERG** stated that based on the advice of clinical experts, it does not consider the company's assumption of persistence of treatment benefits for avapratinib for 5 years to be appropriate. It noted that the risk of death for people discontinuing avapritinib would rapidly increase to a similar risk as the ECM arm (see p.69 ERG report). The ERG base case is a waning duration of 1 month because it gives a close fit to the observed OS data (see p.70 ERG report). A scenario analysis was done by the ERG (range between 1 and 24 months [see p.96 ERG report]).	**The technical team would like the company to provide scenarios exploring a range of treatment waning effect durations.** **The technical team would like clinical expert input on the clinical plausibility of the company and ERG preferred duration of treatment waning.**
7. Utility values in the economic model	**The company** stated that health-related quality of life (HRQoL) data was not collected in the NAVIGATOR trial and no EQ-5D-based or EQ-5D-mappable evidence specific to people with unresectable or metastatic PDGFRA D842V-mutated GIST exists. In the absence of evidence, health-state utility values from previous unresectable or metastatic GIST technology appriasals (TA86, TA179, and TA488) were used to capture the HRQoL as they move through the treatment pathway. The company noted that in a clinical survey, 5/5 (100%) clinicians agreed that the utility values are likely to be reflective of the HRQoL of people with unresectable or metastatic PDGFRA D842V-mutated GIST in current UK clinical practice. In addition, 5/5 (100%) agreed that these values were also likely to be reflective of people in UK clinical practice following the introduction of avapritinib, excluding modifying factors such as adverse events (see p.121 company submission)	**The technical team agree that the utility value for PFS in the 1st line setting is overestimated and that the ERG preferred value of 0.822 should be applied.**

Summary of utility values for cost-effectiveness analysis

	Utility value: mean (standard error)	Reference in company submission	Justification
Progression-free survival			
Avapritinib – 1st line	0.935 (0.094)	page **Error! Bookmark not defined.**	No other evidence available, clinical experts suggest similar burden
Standard of care – 2nd line (sunitinib)	0.781 (0.078)	page **Error! Bookmark not defined.**	
Standard of care – 3rd line (regorafenib)	0.767 (0.077)	page **Error! Bookmark not defined.**	
Progressed disease	0.647 (0.065)	page **Error! Bookmark not defined.**	

The ERG agreed that the utility values for progression-free survival (PFS) for 2nd line and 3rd line, and progressed disease (PD) used by the company appear to be reasonable (see p.75 & 76 ERG report). However, it highlights that the utility value for PFS in the 1st line setting (0.935) is overestimated because this value is higher than the general population utility value of 0.822. The ERG

	preferred utility value for PFS (1st line) is 0.822 (see p.77 & 78 ERG report)	
8. End of life criteria	**The company** stated that avapritinib should be considered as an end of life treatment because: • People receiving ECM have a median overall survival as low as [redacted] months. Based on the inverse probability weighting (IPW) adjusted analysis of the BLU-285-1002 study, [redacted]% of people were still alive at 24 months. In the base case for the economic model, mean OS for those treated with ECM is 23.72 months. • Although median OS was [redacted] in the NAVIGATOR study because the data are not yet mature, at 18 months of follow-up, [redacted]% of patients with the PDGFRA D842V mutation were still alive, with [redacted]% still alive at 42 months. In addition, the economic model indicates that avapritinib would provide an additional [redacted] life-years for people with unresectable or metastatic GIST with the PDGFRA D842V mutation, compared with ECM. [See p.78 & 79 company submission] **The ERG** stated that, on the basis of the evidence presented by the company, it agrees that avapratinib meets the requirements to be considered as an end of life therapy (see p.108).	**The technical team agree that avapritinib could provide an overall survival gain of over 3 months, based on trial evidence and the economic modelled data. In addition, the technical team considers that avapritinib may also meet the short life expectancy criteria. The technical team would like clinical expert input on the life expectance of people with unresectable or metastatic GIST with the PDGFRA D842V mutation who receive established clinical management in the NHS in England.**
9. Cancer Drugs Fund	**The company** acknowledge the uncertainty with respect to overall survival and patient HRQoL. It states that as more data from the ongoing studies NAVIGATOR and VOYAGER become available, uncertainty will be reduced so avapritinib should be placed in the Cancer Drugs Fund (see p.145 company submission)	**At the current value proposition, avapritinib does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000–£30,000 per QALY gained range**

		when commercial arrangements are considered. **The technical team therefore considers that avapritinib does not meet the criteria for inclusion in the Cancer Drugs Fund.** **The technical team acknowledge that the available data are immature. If there was a plausible potential for the technology to be cost-effective, further data from NAVIGATOR and VOYAGER may help to reduce uncertainty.**

2 Questions for engagement

Treatment pathway in economic model

1. Which treatments are used in 1st, 2nd and 3rd line established clinical management in the NHS in England?

2. What proportion of patients receive 1st, 2nd and 3rd line established clinical management in the NHS in England?

Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs

3. Are the populations in the studies generalisable to the population that would be seen in the NHS in England, in terms of prior TKI treatment?

4. Would the treatment effect be similar for people who have received prior therapy with TKIs to those who have not?

Modelling time on treatment

5. Which extrapolation distribution curve best represents the most accurate clinically plausible results for time on treatment?

Extrapolation of overall survival

6. What proportion of patients receiving avapritinib would you expect to be alive at 2, 5 and 10 years?

7. What proportion of patients receiving established clinical management would you expect to be alive at 2, 5 and 10 years?

8. Which extrapolation of overall survival is most clinically plausible?

Extrapolation of progression-free survival

9. Which extrapolation of progression-free survival for 2nd and 3rd line established clinical management is most clinically plausible?

Treatment waning effect

10. What is the most plausible assumption of treatment waning effect for avapritinib?

Utility values in the economic model

11. Which utility value best represents progression-free survival in the 1st line setting?

End of life criteria

12. Under established clinical management (that is, imatinib [1st line], sunitinib [2nd line] and regorafenib [3rd line]), is the life expectancy of people with unresectable or metastatic PDGFRA D842V-mutated GIST more than 24 months?

13. Does avapritinib extend life for more than 3 months for people with unresectable or metastatic PDGFRA D842V-mutated GIST compared with established clinical management?

Cancer Drugs Fund

14. Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?

15. Is avapritinib a good candidate for use in the Cancer Drugs Fund?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **3 September 2020**

Thank you for your time.

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Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

About you

Your name	**Sergio Iannazzo**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Blueprint Medicines GmbH**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Treatment pathway in economic model	
Which treatments are used in 1st, 2nd and 3rd line established clinical management in the NHS in England?	While unresectable or metastatic *PDGFRA* D842V gastrointestinal stromal tumour (GIST) is insensitive to the tyrosine kinase inhibitors (TKIs) currently available, the advice of the clinical experts consulted indicates that eligible patients are not left without a treatment option. Consulted clinical experts from England and Wales stated that they would always inform patients that the available TKIs have a very low probability of being effective for patients with their mutational status, and that they may experience adverse effects, but would still give them the option of receiving treatment as per standard practice. In a survey of clinical experts,[1] most suggested that TKIs were used for treating unresectable or metastatic *PDGFRA* D842V GIST. Furthermore, imatinib, sunitinib and regorafenib have been approved by the National Institute of Health and Care Excellence (NICE),[2-4] are currently reimbursed by the NHS and are recommended in clinical guidelines, as first-, second-, and third-line treatments, respectively, for unresectable or metastatic GIST, regardless of mutation status, which therefore includes patients with *PDGFRA* D842V-mutated GIST.[5-7] Evidence from the NAVIGATOR study further supports the notion that patients with unresectable or metastatic *PDGFRA* D842V GIST currently receive TKIs in clinical practice.[8] During recruitment for the NAVIGATOR study, only **[academic/commercial in confidence information removed]** of patients received avapritinib as a first-line therapy and, of the **[academic/commercial in confidence information removed]** UK-based

	patients, **[academic/commercial in confidence information removed]** were untreated when initiated on avapritinib. Therefore, in a clinical trial recruiting globally, there were few examples of patients with unresectable or metastatic *PDGFRA* D842V GIST going untreated. **Taking this evidence together, although uncertainty remains regarding the current management of patients with unresectable or metastatic *PDGFRA* D842V GIST, it is plausible to assume that the majority of patients in England receive imatinib, sunitinib and regorafenib at first-, second- and third-line, respectively.**
What proportion of patients receive 1st, 2nd and 3rd line established clinical management in the NHS in England?	It is our opinion that the wording of this question will not provide answers that are suitable for the decision problem. This is because, while we agree that in practice some patients with unresectable or metastatic *PDGFRA* D842V GIST may not be treated, this principal also applies to avapritinib. Some patients will be in a condition not conducive to treatment with any TKI, regardless of the efficacy expectation, due to toxicity or tolerability concerns. This will still be the case in first-line treatment after introducing avapritinib to the pathway. Therefore, responses to this question may not be relevant to this decision problem, as the decision problem compares across patients who would be treated with avapritinib if it were made available, which may not include the entire unresectable or metastatic *PDGFRA* D842V GIST population. Consequently, the question should be reframed to ask something more aligned with the decision problem, for example: “of those patients that would be treated with avapritinib, were it to be introduced to the pathway, what proportion would have received first-line imatinib, second-line sunitinib, third-line regorafenib?”, or the responses should be interpreted with this caveat in mind. As stated above, based on our own consultations with clinical experts, our understanding is that most patients in

	England receive TKI treatments, and we use imatinib, sunitinib, and regorafenib in that sequence in line with NICE guidance. In any case, if it is true that only a small proportion of patients receive TKI treatment, we disagree with the assumption that the prognoses of untreated and treated patients are the same, as is implicit in the Evidence Review Group's (ERG's) base-case. Following consultation with clinical experts, the ERG set the market share to 20% for imatinib at first line and to 10% for sunitinib and regorafenib at second- and third-line, respectively. No further adjustment to the model was made, translating to a purely financial impact (i.e. affecting healthcare resource utilization but not patient outcomes). We disagree with this approach, because it is likely that patients receiving best supportive care will have worse outcomes than patients receiving TKIs. This is because treatment decisions are likely to be made on a medical basis rather than essentially at random. If a subset of patients is selected for treatment based on certain characteristics or indicators, then it follows that the characteristics of treated and untreated patients would differ. If patient characteristics differ, then it is reasonable to suggest outcomes would also differ. This supposition is supported by the extrapolated established clinical management (ECM) arm survival in the cost-effectiveness model, which is based on 100% treated patients, being considerably higher than the expectations of the clinical experts consulted separately by both the company and the ERG (see ERG Report Table 27, where clinical experts estimated overall survival to be 5–11% and 0% at 5 and 10 years, respectively, vs. **[academic/commercial in confidence information removed]** and **[academic/commercial in confidence information removed]** survival in the Weibull extrapolation of the ECM arm Kaplan–Meier from BLU-285-1002 at 5 and 10 years, respectively).

	Therefore, either the company comparison should be accepted (all patients in the ECM arm assumed to be treated, with outcomes based on the inverse probability weighting (IPW) analysis of the BLU-285-1002 data), or the outcomes in the ECM arm should be adjusted to reflect the worse outcomes that would be expected in the whole population in comparison with treated population. We therefore believe that the ERG's market share adjustments do not accurately represent the population for this decision problem, and that even if this assumption were to be accepted, then a downward adjustment is required to ECM overall survival to reflect the likely outcomes of patients who are not well enough to justify treatment with currently available TKIs. To facilitate discussion on this matter, the company offer a scenario in their updated base-case results (presented at the end of this document). This scenario reduces the market shares as per the ERG scenario, while also applying a hazard ratio of 1.1 to ECM arm survival, which aims to meet the survival expectations of the clinical experts consulted by the ERG. Although this is exploratory due to a lack of any empirical evidence to substantiate the appropriate hazard ratio, it is the company's hope that this scenario will demonstrate the model's sensitivity to this issue and facilitate discussion on the associated uncertainty.
Issue 2: Generalizability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs	
Are the populations in the studies generalisable to the population that would be seen in the NHS in England, in terms of prior TKI treatment?	Although avapritinib is likely to be used as a first-line treatment for unresectable or metastatic *PDGFRA* D842V GIST in clinical practice, it was not feasible to recruit a sufficiently large sample of first-line patients into a clinical trial due to the extreme rarity of the condition and the regular use of TKIs in clinical practice. As such, **[academic/commercial in confidence information removed]** of patients had received

	prior treatment with imatinib, **[academic/commercial in confidence information removed]** had received prior treatment with sunitinib and **[academic/commercial in confidence information removed]** had received prior treatment with regorafenib. **[academic/commercial in confidence information removed]** patients (**[academic/commercial in confidence information removed]**) had not received any prior TKI therapy and were therefore being treated with avapritinib as a first-line therapy. Consequently, the true overall survival benefit of avapritinib is likely to be underestimated when using the available Kaplan–Meier data because the outcomes of patients treated at first-line are likely to be better than those of patients at later lines, given the ineffective nature of other TKIs. Furthermore, it is logical that patients receiving avapritinib at later treatment lines are less likely to benefit from avapritinib's post-discontinuation treatment effect, which is described in more detail in response to Issue 6. Therefore, results from a cost-effectiveness model based on a simple extrapolation of the Kaplan–Meier data from NAVIGATOR are likely to be highly conservative. Despite these generalizability concerns, the clinical evidence used is the best available evidence at this time. For ECM patients, the data from BLU-285-1002 are the best available evidence. As discussed in response to Issue 1, under the assumption that most patients with D842V GIST are untreated in the UK (which contradicts information we have received from clinical experts), then these patients are likely to outperform those in clinical practice in the UK, and there is therefore substantial uncertainty surrounding the generalizability of BLU-285-1002 data to untreated patients. As mentioned, extrapolation of these data results in an expected survival that is higher than the expectation of the clinical experts consulted by the company and ERG.

	Taken together, the data used have limitations but remain the best evidence available at present. We believe that the decision on avapritinib in this indication should be made using this evidence, with the caveat that there is some resolvable and some unresolvable uncertainty remaining. The direction of bias appears to be unfavourable to avapritinib, because outcomes in BLU-285-1002 are likely better than UK clinical practice, and outcomes in NAVIGATOR are likely worse than UK clinical practice when avapritinib is used as a first-line treatment. The updated company analyses presented at the end of this document explore the uncertainty that results from these biases.
Would the treatment effect be similar for people who have received prior therapy with TKIs to those who have not?	It is typical in an oncological setting that patients at later lines have worse outcomes as they have had the disease for longer, have survived further disease progression, and have survived multiple toxic treatment courses. We suggest that the same is true of patients with unresectable or metastatic *PDGFRA* D842V GIST. The ERG agreed with this notion, stating in their original report: 'We agree with the company's argument as in clinical practice it is generally observed that an effective treatment given in the early course of a disease leads to better survival outcomes'. However, this implied that the ERG's base-case is conservative and, as a result, the statement was subsequently removed from the document. If it is accepted as true that the use of prior (ineffective) therapy leads to worse outcomes, then it is to be expected that the survival outcomes of the NAVIGATOR cohort, of whom approximately **[academic/commercial in confidence information removed]** are treated at first-line,[8] would be worse than that of a cohort treated entirely at first-line.

	Consequently, the survival in NAVIGATOR is likely to be an underestimate compared to UK clinical practice, where avapritinib will primarily be given as a first-line therapy.
Issue 3: Modelling time on treatment	
Which extrapolation distribution curve best represents the most accurate clinically plausible results for time on treatment?	We believe that the hazards for time-on-treatment will reduce over time due to attrition, with healthier patients (i.e. those less likely to discontinue) surviving longer than those in a worse condition at baseline. We are not convinced that the Weibull is able to incorporate the complexity of a reducing hazard. Additionally, when consulting with clinical experts on the final model survival estimates, our original base-case survival extrapolation (Gompertz) was supported. However, we concede that we do not have enough clinical evidence to supersede the advice given in NICE Decision Support Unit Technical Support Document 14. When simply basing a survival distribution decision on statistical and visual fit to the Kaplan–Meier data, a Weibull distribution is a logical selection. Therefore, we agree that it may be reasonable to use a Weibull model in the interest of conservatism.
Issue 4: Extrapolation of overall survival	
What proportion of patients receiving avapritinib would you expect to be alive at 2, 5 and 10 years?	We understand this to be a clinical consultation question and, therefore, defer to the clinical experts on their expected avapritinib patient survival. However, we urge the committee to carefully consider the framing of the question with respect to the decision problem. That is, the expectation of survival for those patients who would be considered for first-line treatment with avapritinib (rather than also considering those patients that are not well enough to be treated with any TKI) with and without avapritinib as an available

	therapy. The experts consulted during the initial submission agreed that the survival outcomes in the base-case company model were plausible for the population who would be treated with avapritinib in UK clinical practice.
What proportion of patients receiving established clinical management would you expect to be alive at 2, 5 and 10 years?	The experts we consulted during the initial submission agreed with the final modelled patient outcomes in the ECM arm.[9] The clinical experts consulted by the ERG estimated survival at 5–11% and 0% at 5 and 10 years, respectively, (ERG Report Table 27) which is lower than survival observed in the Weibull extrapolation of the ECM arm Kaplan–Meier from BLU-285-1002. As above, we consider this a question for clinical expert consultation rather than a technical modelling issue and urge the Committee to carefully consider the framing of the question to the experts.
Which extrapolation of overall survival is most clinically plausible?	We have provided several models of overall survival for the consideration of the Committee, ERG and NICE Technical Team. These include: • Extrapolation of NAVIGATOR overall survival for patients with unresectable or metastatic *PDGFRA* D842V GIST, censoring for treatment discontinuation (Company Submission) • Standard extrapolation of uncensored NAVIGATOR overall survival for patients with unresectable or metastatic *PDGFRA* D842V GIST (in response to ERG clarification question B1)

	• Modelled overall survival when implementing a linearly diminishing post-discontinuation treatment effect of various durations (in response to ERG clarification question B2) We would encourage the Committee to consider the magnitude of the uncertainty surrounding avapritinib long-term survival by reviewing all of these. However, we maintain our position that the most appropriate method is to explicitly model the post-discontinuation treatment effect of avapritinib by linking time on treatment to overall survival, as this was incorporated based on the advice of clinical experts. Further evidence in support of this is presented in response to Issue 6. For convenience, below is the scenario analysis we presented in response to ERG clarifications, presenting the impact of different post-discontinuation treatment effect durations. **[academic/commercial in confidence information removed]** **Key:** AVA, avapritinib; ECM, established clinical management.
Issue 5: Extrapolation of progression-free survival	
Which extrapolation of progression-free survival for 2nd and 3rd line established clinical management is most clinically plausible?	We believe that there is substantial uncertainty surrounding the appropriate extrapolation of progression-free survival for second- and third-line ECM, but we agree that the ERG's approach is reasonable.
Issue 6: Treatment waning effect	
What is the most plausible assumption of treatment waning effect for avapritinib?	Firstly, we would like to clarify that the model does not include a treatment waning effect but a post-discontinuation treatment effect. A treatment waning effect is the loss of efficacy in the whole cohort regardless of whether patients are on treatment or not. This

	can only reduce overall survival (when comparator survival is inferior) because the hazard applied can only increase from that of the intervention arm's overall survival, which does not censor for discontinuation. Conversely, with a post-discontinuation treatment effect, treatment benefit is maintained beyond the period of treatment per the time on treatment analysis. This can both increase and decrease overall survival, depending on overall survival discontinuation censoring, time on treatment and post-discontinuation treatment effect duration. If the control arm's overall survival is a reasonable representation of off-treatment overall survival in the intervention arm, then setting the period of post-discontinuation treatment effect to 0 (or a very short duration) will create an extrapolation which visually aligns with the overall survival Kaplan–Meier not censoring for discontinuation. Additionally, when the Kaplan–Meier is immature, this post-discontinuation treatment effect approach will result in a lower extrapolated tail – similar to that of a treatment waning effect. However, when the post-discontinuation treatment effect duration is increased, the overall survival in the intervention arm will change in both rate and shape as a result, depending on the on-treatment overall survival Kaplan–Meier in the intervention arm and the assumed post-discontinuation treatment effect duration. In our original base-case, we assumed that the avapritinib post-discontinuation treatment effect endures for 60 months, using linear interpolation to gradually reduce the treatment effect over that period for discontinued patients within the tunnel state. This was implemented with the support of clinical experts, who evaluated the final modelled overall survival and suggested that our estimations were plausible for first-line patients. On reflection, and upon reviewing clinical opinion from previous NICE technology appraisals (TAs) in TKIs, we appreciate that this could be seen to be optimistic.

	Our updated base-case assumes a post-discontinuation treatment effect of 18 months rather than 60 months. This value is slightly below the midpoint between two suggestions provided in recent TKI NICE appraisals, TA621 (osimertinib) and TA463 (cabozantinib). In both cases, clinical experts suggested that the benefit of TKI treatment extends beyond the period of active treatment, as the tumour(s) continue to shrink. In other appraisals of TKIs, clinical opinion on duration of treatment effects after discontinuation was not reported, possibly because of the frequent use of models that do not simulate discontinuation explicitly. Therefore, we consider the estimates from TA621 and TA463 to be the best indication of two extremes: NICE TA621: Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer Final appraisal determination: Section 3.5 The clinical experts agreed that because osimertinib is associated with improved progression-free survival and duration of response, treatment effect would continue after symptomatic and radiological progression for some people. **They stated that this could plausibly give about 3 months of additional benefit after stopping treatment with osimertinib compared with erlotinib and gefitinib.** NICE TA463: Cabozantinib for previously treated advanced renal cell carcinoma Final appraisal determination: Section 4.17 The committee noted that both the company and the ERG assumed that the effect of cabozantinib continued beyond the trial follow-up, even after the disease progressed or

	patients stopped treatment, but the committee was not presented with evidence to support this. The clinical experts considered that it was not clear whether a survival benefit would continue after stopping treatment. **They explained that, in clinical practice, some patients have stable disease for 2 to 3 years after stopping treatment, whereas the disease progresses more quickly in others**. Also, some patients have a prolonged response after a short length of treatment and others do not. The committee concluded that assuming the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain. One additional relevant example is provided in NICE TA451, where it was assumed that patients achieving a complete cytogenetic response (CCyR; approximately 60% of the cohort) permanently maintained the benefit (a better survival and a lower progression rate) even after treatment discontinuation. This assumption was considered plausible by clinical experts and was not criticized in the appraisal. The suggestion that TKI treatments such as avapritinib have a benefit that extends beyond the treatment period is not novel, and clinical experts have indicated that this effect has also been observed for patients treated with avapritinib. In an advisory board, clinical experts suggested that the mechanism of the observed prolonged responses could be driven by an anti-vascular effect, followed by calcification of the tumours.[10] To further support the claim for a prolonged treatment effect, an abstract written by a clinical expert, which summarizes two separate case studies demonstrating a post-discontinuation treatment effect for avapritinib, is submitted as supplementary material for consideration (academic-in-confidence until publication). Importantly, the author concludes that 'avapritinib is not only highly active in advanced *PDGFRA* exon 18 mutant

	GIST, but also changes the natural course of D842V-mutated GIST after treatment cessation, with progressive volumetric regression of residual lesions, specific radiographic changes and prolonged patient benefit' and that 'discontinuous, shorter-term or intermittent administration of avapritinib may be associated with good clinical outcome in advanced disease'.[11] This suggests that avapritinib confers a post-discontinuation treatment effect which would not be fully captured in the NAVIGATOR data, given the frequent use of prior TKIs and short-term follow-up. Whether this post-discontinuation treatment effect would be experienced by patients discontinuing avapritinib due to disease progression is not known. However, of the patients who permanently discontinued avapritinib treatment during the NAVIGATOR study, only **[academic/commercial in confidence information removed]** discontinued due to disease progression, with **[academic/commercial in confidence information removed]** discontinuing due to toxicity, suggesting that this would represent the minority of discontinuations. While the concept of a post-discontinuation treatment effect for avapritinib patients is broadly accepted by clinicians, there is a large amount of uncertainty surrounding the post-discontinuation treatment effect duration for avapritinib patients. In the absence of any reliable data, we have simply used 18 months as an approximate midpoint between the 3-month and 3-year estimates from TA621 and TA463. We appreciate that this assumption is associated with considerable uncertainty and therefore include additional scenario analyses placing the effect at 3 months and 3 years for committee consideration of the range of impacts. However, we would posit that an 18-month post-discontinuation treatment effect duration is more plausible than the 1-month post-discontinuation treatment effect duration in the ERG's base-case given that (i) the ERG's assumption

	results in a worse survival outcome than a simple extrapolation of the NAVIGATOR overall survival Kaplan–Meier, (ii) the NAVIGATOR overall survival Kaplan–Meier is likely to underestimate survival of patients receiving avapritinib in clinical practice, due to the higher use of prior TKIs in NAVIGATOR than would be expected in clinical practice, and (iii) clinical testimony and evidence both suggest that TKIs in general and avapritinib specifically have a post-discontinuation treatment effect lasting a considerable period of time.
Issue 7: Utility values in the economic model	
Which utility value best represents progression-free survival in the 1st line setting?	We do not question the amendment to the first-line health state utility value for patients. We used the best available information but accept that this is above the general population level of health-related quality of life, so we accept the ERG's proposed change. However, we do question the exclusion of the data from VOYAGER in the ERG's base case. While we accept that we submitted these data post-submission at clarification questions stage (when available to us per the VOYAGER data cut), these data are (i) in the relevant patient population, (ii) more up-to-date than alternatives, and (iii) based on a relatively large sample (n=385 patients) We therefore cannot see any justification for this to not be incorporated into both the company and ERG base-case assumptions. Consequently, our updated base case uses the VOYAGER utilities for third-line and progressed disease states, while applying the general population cap for first-line patients.
Issue 8: End of life criteria	

Under established clinical management (that is, imatinib [1st line], sunitinib [2nd line] and regorafenib [3rd line]), is the life expectancy of people with unresectable or metastatic PDGFRA D842V-mutated GIST more than 24 months?	We consider this issue to be a direct contradiction to the framing of Issue 1, which supposes that not all patients are treated. In contrast, the framing of this question implies that ECM is first-line imatinib, second-line sunitinib and third-line regorafenib. If it is true that some patients are not deemed suitable for current TKI treatment, then the reasons for this are likely to be related to their prognosis. It is logical to assume that untreated patients would have a worse prognosis than treated patients, because (i) healthier patients are likely to be selected for treatment, as they would be more likely to tolerate related adverse events, and (ii) there may be a marginal physiological or psychological benefit of treatment with available TKIs. As the prognosis of treated patients is likely to be better than that of untreated patients, considering only the life expectancy of treated patients could create bias against avapritinib reaching the criteria as an end-of-life life-extending therapy. In the ERG report, the ERG agreed that this indication should be considered to meet end-of-life life-extending criteria, and that avapritinib extends life on average more than 3 months. Both the company and the ERG consulted with clinical experts, who expect ECM overall survival to be considerably below 2 years in the median (and mean). The median overall survival in the cost-effectiveness model is approximately **[academic/commercial in confidence information removed]** months, and this is likely to be an overestimate for the reasons stated in response to Issue 1 and above. Therefore, we consider avapritinib to meet the NICE end-of-life life-extending criteria in this indication.

Does avapritinib extend life for more than 3 months for people with unresectable or metastatic PDGFRA D842V-mutated GIST compared with established clinical management?	We, the ERG, and the clinical experts consulted by both parties agree that the expected overall survival of ECM patients is under 2 years and that avapritinib will increase this by considerably more than 3 months. This is supported by even the most conservative ERG estimates of overall survival benefit, which are considerably more than 3 months.
Issue 9: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	Yes. Entry of avapritinib into the Cancer Drugs Fund (CDF) will enable a more informed determination of cost-effectiveness. Currently, the available Kaplan–Meier data are immature, leading to considerable uncertainty surrounding expected and median survival in avapritinib patients. The increase in follow-up on overall survival data should allow NAVIGATOR to at least approach median overall survival, while meeting median progression-free survival and time-on-treatment. This will considerably reduce the remaining uncertainty, allowing more reliable extrapolations and an improved determination of cost-effectiveness. **[academic/commercial in confidence information removed]** potentially adding more patients with unresectable or metastatic *PDGFRA* D842V GIST treated at first-line with avapritinib to the pool for analysis. Depending on the number of first-line patients recruited in this registry, this may reduce the need to link outcomes and to simulate the post-discontinuation treatment effect explicitly, as the increased completeness of the data will reduce the error/bias present when not linking them. Finally, additional data will be available on dosing and dose breaks, which will address the uncertainty surrounding the dosing regimen of avapritinib utilized by clinicians in practice, as described in more detail below.

Is avapritinib a good candidate for use in the Cancer Drugs Fund?	Yes. Avapritinib represents a step change in therapy for patients with unresectable or metastatic *PDGFRA* D842V GIST because of its substantial overall survival benefit, the extent of which is rarely seen in oncology products. We accept that substantial uncertainty remains with regards to the survival benefit, post-discontinuation treatment effect duration, and dosing regimen used in clinical practice (see below); additional data collection in the CDF (**[academic/commercial in confidence information removed]**) will reduce the uncertainty surrounding each of these key points. Furthermore, as shown in our revised economic analysis, there are several plausible incremental cost-effectiveness ratios (ICERs) for avapritinib that lie below the threshold for cost effectiveness, given that avapritinib meets the criteria as an end-of-life life-extending therapy.
Additional Evidence	
Update data cut from NAVIGATOR	To align with the data included in the summary of product characteristics, we have incorporated the latest data cut from NAVIGATOR and will provide updated results in our updated economic analysis.
Alternate-day dosing pattern	Recent information provided by a UK-based clinical expert has indicated that some clinicians may use an alternate-day dosing pattern for avapritinib in clinical practice, where patients take a tablet of avapritinib at the same concentration every other day. This has also been supported by several other international clinical experts at an advisory board.[10] Clinicians who have used this alternate-day dosing have done so without observing loss of efficacy. Indeed, an abstract written by a clinical expert, which summarizes two separate case studies of patients treated with avapritinib (submitted as supplementary material as academic-in-confidence until publication), concludes that 'discontinuous, shorter-term or intermittent administration of avapritinib may be associated

	with good clinical outcome in advanced disease'.[11] Taken together, this information suggests that treatment breaks are likely to be more commonly used in clinical practice than in NAVIGATOR to manage toxicity without efficacy loss. Based on this, we have provided additional analysis to explore the cost effectiveness of avapritinib if an alternate-day dosing pattern was used in clinical practice. The relative dose intensity (RDI) used in the cost-effectiveness model reflects the 'doseable' days compared to dosed days during NAVIGATOR follow-up for patients still classed as on treatment (**[academic/commercial in confidence information removed]**). For this updated analysis, we have simply altered the cell labelled RDI in the model for avapritinib from **[academic/commercial in confidence information removed]** to 50% to test the impact of alternate-day dosing, assuming no loss of efficacy. We accept that the reality of this practice is uncertain but feel that it is important to explore the magnitude of the uncertainty surrounding this, given the indication from clinical experts that this is likely to occur in clinical practice, and believe this uncertainty should be considered..

Updated base-case analysis

As part of technical discussions with the ERG and NICE technical team (TT), we are submitting a revised base-case for our economic analysis, considering the updated data-cut from NAVIGATOR and the evidence and arguments presented by both the ERG and TT. Our intention is to progress the discussion surrounding the cost-effectiveness of avapritinib to maximize the possibility of a determination being made at the first appraisal meeting, as per the direct request of the Chair of the NICE technical engagement call.

Table 1 provides a side-by-side comparison of our original base-case assumptions and updated base-case assumptions. Overall, we agree with the arguments of the ERG and NICE TT. However, on the points of post-discontinuation treatment effect duration, market shares applied to ECM treatments and health state utility values, we disagree with the ERG and TT approaches as outlined in the responses above. Furthermore, as clinical experts have indicated that alternate-day dosing of avapritinib is a plausible scenario for UK clinical practice, we present this as a separate base case analysis throughout this section.

Table 1: Updated base-case assumptions

Model setting		Original base case	Updated base-case
% of patients receiving ECM arm			
	1L imatinib	100%	100%
	2L sunitinib	100%	100%
	3L regorafenib	100%	100%
OS			
	Post-discontinuation treatment effect duration	60 months	18 months
	Extrapolation of avapritinib arm	Log-normal	Weibull
	Extrapolation of ECM arm	Weibull	Weibull
PFS			
	Extrapolation of avapritinib arm	Weibull	Weibull
	Extrapolation of ECM: 1L	Weibull	Weibull
	Extrapolation of ECM: 2L	Log-logistic	Weibull
	Extrapolation of ECM: 3L	Gompertz	Weibull
ToT			
	Data for ToT for avapritinib arm	Censored for deaths	Same as PFS
	Extrapolation of avapritinib arm	Gompertz	Weibull
Mortality			
	General population all-cause mortality	ONS 2015-2017	ONS 2016-2018

Model setting		Original base case	Updated base-case
Utilities	PFS 1L	0.935	0.822
	PFS 2L	0.781	0.781
	PFS 3L	0.767	0.782
	PD	0.647	0.727
Resource use	% of patients for resources used for PD state	Company assumptions	ERG assumptions
Alternate-day dosing assumption	Assume alternate-day dosing?	No	Presented with and without this assumption
Data cut	Data-cut used for the analysis	January 2020, Per Document B	Updated March 2020

Key: PD, progressed disease; ECM, established clinical management; 1L, first line; 2L, second line; 3L, third line; ONS, Office of National Statistics; ToT, time on treatment; PFS, progression-free survival; Doc B, NICE submission document B; OS, overall survival; TKI, tyrosine kinase inhibitor.

Table 2 reports the base-case results with and without the assumption of alternate-day dosing. As shown, the updated base-case ICERs are £45,954 and £80,342 with and without alternate-day dosing, respectively. When considering alternate-day dosing, the updated base case is below the NICE cost-effectiveness threshold when end-of-life life-extending criteria are met. Therefore,

dosing in real clinical practice should be considered an issue of high importance to the cost-effectiveness case of avapritinib in patients with unresectable or metastatic *PDGFRA* D842V GIST.

Table 2: Base case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
New base case (no alternate-day dosing)							
ECM	**[academic / commercial in confidence information removed]**	1.77	**[academic / commercial in confidence information removed]**				
Avapritinib	**[academic / commercial in confidence information removed]**	8.58	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	6.81	**[academic / commercial in confidence information removed]**	80,342
New base case (alternate-day dosing)							
ECM	**[academic / commercial in confidence information removed]**	1.77	**[academic / commercial in confidence information removed]**				

Avapritinib	**[academic / commercial in confidence information removed]**	8.58	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	6.81	**[academic / commercial in confidence information removed]**	45,954
Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.							

Table 3 and Table 4 present breakdowns of quality-adjusted life years and life years gained, respectively. Avapritinib is associated with approximately a 3-year gain in progression-free survival compared to ECM and also a considerable gain in survival in progressive disease, while the absolute survival in second-line and third-line states are similar across arms owing to our conservative assumption of equality of progression rate (but not death rate) in those states.

Table 3: Summary of QALY gain by health state (discounted)

Health state	Avapritinib	ECM	Incremental QALYs	Absolute increment	% absolute increment
PF 1L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PF 2L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PF 3L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PD	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Disutility due to AE	-0.01	0.00	-0.01	0.01	**[academic / commercial in confidence information removed]**

Total	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	100%

Key: 1L, first line; 2L, second line; 3L, third line; AE, adverse event; ECM, established clinical management; PD, progressed disease; PF, progression-free; QALY, quality-adjusted life year.

Table 4: Summary of life year gain by health state (discounted)

Health state	Avapritinib	ECM	Incremental LYs	Absolute increment	% absolute increment
PF 1L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PF 2L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PF 3L	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
PD	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Total	8.58	1.77	6.81	6.81	100%

Key: 1L, first line; 2L, second line; 3L, third line; AE, adverse event; ECM, established clinical management; LY, life year; PD, progressed disease; PF, progression-free.

Table 5 presents a cost breakdown with and without alternate day dosing.

Table 5: Summary of predicted resource use by category of cost (PAS price, discounted)

Item	Avapritinib	ECM	Incremental costs	Absolute increment	% absolute increment
New base case (no alternate dosing)					
Avapritinib	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Other TKIs	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
HCRU	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
EoL	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**

AEs	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Total	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
New base case (alternate dosing)					
Avapritinib	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Other TKIs	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
HCRU	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**

EoL	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
AEs	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**
Total	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**

Key: AE, adverse event; ECM, established clinical management; EoL, end of life; HCRU, health care resource use; PAS, patient access scheme; TKI, tyrosine kinase inhibitor.

Probabilistic sensitivity analysis results are presented in Table 6. These provide similar results to the deterministic ICER, with slight increases in the ICER both with and without alternate-day dosing, which are attributable to asymmetric distributions of survival.

As shown in Figure 3 and Figure 4, at a willingness-to-pay threshold of £50,000/quality-adjusted life year gained, avapritinib has a 1.4% and a 53.9% chance of being cost effective using the new base case, without and with alternate-day dosing, respectively, at the patient access scheme price.

Table 6: Sensitivity analysis results comparison (discounted, with PAS)

Technology	Total costs (£)		Total QALYs		ICER (£/QALY)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
New base case (no alternate dosing)						
ECM	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**		
Avapritinib	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	85,462	80,342
New base case (alternate dosing)						
ECM	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**		
Avapritinib	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	**[academic / commercial in confidence information removed]**	48,410	45,954

Technical engagement response form

Key: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 1: Cost-effectiveness plane (1,000 probabilistic sensitivity analysis runs; discounted, with PAS) – new base case (without alternate-day dosing)

[academic/commercial in confidence information removed]

Key: CE, cost-effectiveness; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 2: Cost-effectiveness plane (1,000 probabilistic sensitivity analysis runs; discounted, with PAS) – new base case (with alternate-day dosing)

[academic/commercial in confidence information removed]

Key: CE, cost-effectiveness; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 3: Cost-effectiveness acceptability curve – avapritinib (discounted; with PAS) – new base case (without alternate-day dosing)

[academic/commercial in confidence information removed]

Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 4: Cost-effectiveness acceptability curve – avapritinib (discounted; with PAS) – new base case (with alternate-day dosing)

[academic/commercial in confidence information removed]

Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Finally, Table 7 reports the results of our scenario analysis based on the updated base case. Scenarios, exploring uncertainty related to the issues considered in the Technical Report, range from cost-effective to not cost-effective, with several scenarios resulting in an ICER below the £50,000 end-of-life cost-effectiveness threshold. This demonstrates the magnitude of uncertainty and sensitivity of the model results to the dosing schedule given to patients in clinical practice. Taken together, when considering how avapritinib is likely to be used in practice, avapritinib is cost-effective in the base-case and most other scenarios and that inclusion in the CDF is likely to resolve a substantial proportion of the remaining uncertainty.

Table 7: Scenario analysis, starting from the updated base case, without and with alternate-day dosing

Scenario	ICER (without alternate-day dosing)	ICER (with alternate-day dosing)
Base case	£80,342	£45,954
Treatment waning: 3 months	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
Treatment waning: 36 months	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
ECM TKIs from BLU-285-1002	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
OS avapritinib: log logistic	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
PFS avapritinib and ECM: per original company base-case	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
ERG preferred health-state utility values	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
General population cap not applied to health-state utility values	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**
ECM TKIs as in ERG base case with reduced OS (HR=1.1)	**[academic/commercial in confidence information removed]**	**[academic/commercial in confidence information removed]**

Key: ECM, established clinical management; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal – Supplementary evidence

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [ID1626]

Supplementary evidence, updated data-cut from NAVIGATOR study

August 2020

1 New evidence submission, longer follow up

As the extrapolation of overall survival (OS), progression-free survival (PFS) and duration of treatment are crucial to the appraisal of avapritinib in D842V gastrointestinal stromal tumours (GIST), we believe it is important to use the most recent available data with the longest duration.

The use of the latest available data cut-off will allow alignment between NICE technology appraisal and the regulatory process with the European Medicines Agency (EMA). Also, this will likely reduce the amount of clinical data marked as CiC or AiC, as these clinical data will be publicly available in EMA European Public Assessment Report (EPAR).

The latest available data cut-off date is March 2020, and the median follow-up is 25.5 months, as compared with the median follow-up of 22.8 months in the data currently used in the model.

2 Consideration of dosing patterns in the clinical practice

As an additional new element, we plan to include analyses that consider possible dosing patterns in real-world UK clinical practice after the approval of avapritinib. Clinicians involved in the early use of the treatment adopted in some cases an alternate-day dosing pattern to improve the tolerability of the drug. This was initiated with the clinical objective of providing a better control over adverse events (AEs), and clinicians have also reported unaltered control of the disease. This suggests that implementation of the alternate-day dosing pattern with preserved treatment efficacy is a plausible real-world scenario, which should be explored within the economic analysis. Case reports will be provided to support these analyses. This evidence will additionally support the concept of a sustained effect beyond treatment discontinuation.

According to the information provided by clinicians (both UK and ex-UK), we believe that this type of dosing will be frequently implemented in UK clinical practice. Therefore, we would like to add this aspect into the economic analysis for a more

accurate cost calculation, especially considering that this may have the potential to influence the ICER of avapritinib. Conditional approval via the CDF could help to alleviate the substantial uncertainty surrounding dosing patterns, through observation of the actual dosing patterns used in practice, and any impact of these on clinical efficacy.

My responses are in blue- Charlotte Benson

1. **Treatment waning effect:** In its base case, the company model assumes a survival advantage with avapritinib compared with established clinical management 5 years after stopping treatment. The ERG think that this is not plausible and believe this would be 1 month after stopping treatment.
    - In your opinion, what would you expect the treatment waning effect with avapritinib to be?

   Currently there is no data in the public domain to support this statement.

2. **Treatment pathway:** The company base case economic model for the PDGFRA D842V-mutated GIST treatment pathway is set out as below:

    - Intervention arm: Avapritinib (1st line), Standard of Care (SoC) at 2nd line and SoC at 3rd line
    - Comparator arm: Established clinical management (ECM), which comprises imatinib (1st line), sunitinib (2nd line) and regorafenib (3rd line)

   The ERG notes that in the company's clinical studies, the majority of patients received prior tyrosine kinase inhibitors (TKI's) whereas in UK clinical practice they would expect that most patients would receive best supportive care. The ERG believe that few patients would receive TKIs in clinical practice. They estimated 20% of patients would receive imatinib and fewer than 10% of patients would receive sunitinb and regorafenib.

   In your opinion:

    - What treatments would be used 1st, 2nd and 3rd line in established clinical management for patients with the PDGFRA D842V mutation?
    - In those patients with established PDGFRA D842V mutation treated in a Sarcoma (GIST) Centre very few would be treated with standard 1st, 2nd or 3rd line treatments. Particularly as a compassionate use programme for Avapritinib is currently available. Whilst it is advised via NICE guidelines that patients with GIST are treated in Specialist centres and have pathology review including mutational analysis, a small number of patients with GIST are still treated by non-Sarcoma specialists. Not all of those patients have specialist pathology review and mutational analysis of the KIT and PDGFRA genes performed. Therefore, a very small number of patients with D842V mutations may be undiagnosed and receive imatinib/sunitinib/regorafenib as per standard GIST paradigm. As the total population of patients with D842V mutations is small, this proportion is very small.
      For those that are diagnosed with D842V mutation but are not able to access Avapritinib compassionate use programme (currently open in London) a small number might be offered imatinib. There is a retrospective cohort study of patients with PDGFRA Exon 18 mutations that showed of those with D842V mutations 2 out 16 patients responded to imatinib (12.5%) (Eur J Cancer 2017 May;76:76-83. doi: 10.1016/j.ejca.2017.02.007). However, where Avapritinib is available this would be used in preference to imatinib.

    - What proportions of PDGFRA D842V patients would receive imatinib, sunitinib, regorafenib and/or best supportive care?
      In the absence of Avapritinib then patients with good Performance status might be offered imatinib to see if therapeutic benefit (as per study referenced above). However sunitinib and regorafenib are very unlikely to be offered following imatinib in Specialist Sarcoma Centres where the presence of the mutation is known. Those with progression on imatinib would be offered Best supportive care or clinical trial if available.

3. **Prior use of TKIs in the trial populations:** The company clinical studies allowed patients to receive TKIs prior to treatment with avapritinib or established clinical management (ECM) but stated that the population was reflective of the unresectable or metastatic PDGFRA D842V-mutated GIST

population that they would see in clinical practice. The ERG noted that patients received more frequent prior TKI use than would be expected in UK clinical practice.

In your opinion:

- Are the populations in the studies generalisable to the population that would be seen in the NHS in England, in terms of prior TKI treatment?

  Largely yes. It is probable in the UK that fewer patients will have received prior TKI than in the published study (Lancet Oncol 2020; 21: 935–46) while some will have received one prior line only (imatinib) and therefore will be of better performance status.

4. **End of Life:** In the company base case for the economic model, mean overall survival for those treated with ECM is 23.72 months.

In your opinion:

- What is the life expectancy for people with the PDGFRA D842V mutation after initial diagnosis?

  OS is approximately 15 months for those with advanced disease

  (Clin Cancer Res 2012; 18: 4458–64.; Cancer Res Treat 2016; 48: 546–52.; Hum Pathol 2002; 33: 466–77.)

- Does the presence of the PDGFRA D842V mutation change the prognosis compared with people without the mutation?

  Retrospective data shows that patients with PDGFRA mutations have been shown to generally have more indolent disease compared with patients with KIT mutations Retrospective studies have also suggested that PDGFRA mutant GIST are significantly more often very low/low risk compared with KIT mutants (49 vs 26%), more often had tumours in the stomach (91 vs 45%) and more frequently (70 vs 42%) had <5 mitoses per 50 high power field compared with KIT mutant GIST (Ann. Oncol. 23(2), 353–360 (2012)

  In a large European retrospective cohort across 12 institutions, PDGFRA mutations were found in 11% patients, with only a small proportion (12.5%, 44/365) of these patients developing metastatic disease (Int J Mol Sci 2018; 19: 732.). In a separate large study of 1056 patients with localized GIST who underwent surgery, 148 patients had PDGFRA mutations (13.6%). Patients with tumours with PDGFRA mutations had a significantly better disease-free survival compared with those with KIT exon 9 and 11 mutations (median disease-free survival, not reached vs 45.5 months, respectively). There was no difference in outcome when PDGFRA D842V mutants were compared with all other PDGFRA mutants (Clin. Cancer Res. 20(23), 6105–6116 (2014).)