Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Blueprint Medicines:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Joint submission from The UK Mastocytosis Support Group & Leukaemia Care – co-authored by patient expert Jess Hobart
   b. British Society of Allergy and Clinical Immunology

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**
   a. Company response
   b. Addendum

7. **Technical engagement responses and statements from experts:**
   a. Dr Andrew Whyte – clinical expert, nominated by Royal College of Physicians and British Society for Allergy & Clinical Immunology
   b. Dr Jonathan Lambert – clinical expert, nominated by Blueprint Medicines Corp and UK Mastocytosis Support Group
   c. Andrew Dugdale – patient expert, nominated by UK Mastocytosis Support Group *(not attending committee meeting)*
   d. Sue Rudland - patient expert, nominated by UK Mastocytosis Support Group

8. **Technical engagement response from stakeholders**
   a. The UK Mastocytosis Support Group
   b. British Society of Haematology (BSH)

9. **External Assessment Group critique of company response to technical engagement** prepared by Centre for Reviews and

Dissemination and Centre for Health Economics – York

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 advanced systemic mastocytosis [ID3770]

Document B

Company evidence submission

05 February 2024

File name	Version	Contains confidential information	Date
ID3770 Avapritinib Document B	**V4**	**Yes**	**06 February 2024**

Contents

Tables and figures

List of abbreviations

1L	First line of therapy (patients who have not received prior systemic therapy)
2L+	Second or later line of therapy (patients who have received one or more prior systemic therapies)
AdvSM	Advanced systemic mastocytosis
AdvSM-SAF	AdvSM Symptom Assessment Form
AE	Adverse events
AESI	Adverse events of special interest
AHN	Associated haematologic neoplasm
AIC	Akaike information criterion
AIM	American Initiative in Mast Cell Diseases
Allo-HSCT	Allogeneic haematopoietic stem cell transplant
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
BAT	Best available therapy
BIC	Bayesian information criterion
BM	Bone marrow
BNF	British National Formulary
CD	Cluster of differentiation
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMML	Chronic myelomonocytic leukaemia
CR	Complete remission
CSR	Clinical study report
CUP	Compassionate Use Program
DHSC	Department of Health and Social Care
DOR	Duration of response

DOT	Duration of treatment
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
ECS	External control study
ED	Emergency department
EMA	European Medicines Agency
EOS	End of study
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life 30-Item Core Questionnaire
FDA	US Food & Drug Administration
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumour
HCHS	Hospital and community health services
HCP	Healthcare professionals
HES	Hospital Episode Statistics
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HSUV	Health state utility values
HTA	Health technology assessment
ICC	International Consensus Criteria
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient-level data
IPSM	International Prognostic Scoring System in Mastocytosis
IPTW	Inverse probability of treatment weights
ISM	Indolent systemic mastocytosis

ITC	Indirect treatment comparison
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue
KM	Kaplan-Meier
LOT	Lines of treatment
LY	Life years
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MARS	Mutation-Adjusted Risk Score
MC	Mast cell
MCID	Minimal clinically important difference
MCL	Mast cell leukaemia
MCS	Mental component score
MDS	Myelodysplastic syndrome
MF	Myelofibrosis
MHRA	Medicines & Healthcare products Regulatory Agency
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerable dose
NA	Not available
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NHB	Nett health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not recorded
OD	Once daily
ONS	Office of National Statistics
OR	Odds ratios
ORR	Overall response rate

OS	Overall survival
PartSA	Partition survival analysis
PAS	Patient access scheme
PASLU	PAS Liaison Unit
PCS	Physical component score
PD	Progressive disease
PDGFRA	Platelet-derived growth factor receptor alpha
PF	Progression-free
PFS	Progression-free survival
PGIS	Patient Global Impression of Symptom Severity
PPR	Pure pathological response
PPRE	Pure Pathological Response-Evaluable
PR	Partial remission
PRISM	Perceptions, Realities and Insights on Systemic Mastocytosis
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unity
QALY	Quality-adjusted life years
QoL	Quality of life
RAC-RE	Response Assessment Committee Response-Evaluable
RCT	Randomised controlled trials
RDI	Relative dose intensity
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with associated haematologic neoplasm
SmPC	Summary of product characteristics
SoC	Standard of care

SSC	Study steering committee
SSM	Smouldering systemic mastocytosis
STA	Single technology appraisal
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TOT	Time on treatment
TRAE	Treatment-related adverse events
TSS	Total symptom score
TtNTL	Time to next treatment line
TTO	Time Trade-Off
TTR	Time to response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAF	Variant allele fraction
WDSM	Well-differentiated systemic mastocytosis
WHO	World Health Organization

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 authorisation for this indication.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced systemic mastocytosis	Adults with advanced systemic mastocytosis	Not applicable
Intervention	Avapritinib	Avapritinib	Not applicable
Comparator(s)	• Midostaurin • Cladribine • Imatinib • Interferon alpha	• Midostaurin • Cladribine	The main comparator for avapritinib is midostaurin. Midostaurin is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL),[1] and is recommended by NICE in this indication. ASM, SM-AHN and MCL are collectively known as advanced systemic mastocytosis (AdvSM). No other treatments have regulatory approval in the UK or are recommended by NICE for the treatment for AdvSM. Midostaurin is therefore the current standard of care and constitutes established clinical practice for patients with AdvSM in England.[2,3]

			Off-label cladribine is no longer commonly used to treat patients with AdvSM in the UK but may be used in patients who require rapid debulking or in patients who have to discontinue midostaurin due to tolerability issues. Data comparing avapritinib treatment with cladribine as second- or further-line (2L+) treatments have been included in this submission. Imatinib is not considered a relevant comparator for avapritinib in this submission. It is not routinely commissioned in the NHS in England for AdvSM and is used as an off-label therapy in a very small number of patients (2-3%) that do not have an activating *KIT* mutation (specifically the *KIT* D816V mutation which is responsible for approximately 95% of AdvSM cases).[4] In analysis of Hospital Episode Statistics (HES) data (1 April 2018 to 31 March 2023), other than midostaurin, [redacted] of tyrosine kinase inhibitors (TKIs) for the treatment of AdvSM, including imatinib, was identified. It is noted that treatment for AdvSM may also include off-label use of pegylated interferon alpha, however, this treatment does not target the underlying cause of the disease has limited efficacy.[5,6] Use of pegylated interferon alpha in the UK is extremely limited (4% of known lines of therapy in the real-world study were with pegylated interferon alpha).[2,7] Whilst this submission does not include comparisons with imatinib and interferon alpha individually, they are represented in a comparison of outcomes in patients treated with best available therapy (BAT), which includes midostaurin and cladribine, as well as other off-label therapies not included in the scope of this submission.

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • symptom severity • adverse effects of treatment • health-related quality of life.	The following outcomes are presented: • overall survival • progression-free survival • response rate • symptom severity • adverse effects of treatment • health-related quality of life • measures of mast cell burden	The outcome measures to be included in the company submission are in line with the final scope. In addition to the outcomes in the scope, measures of mast cell burden have been included to provide important additional evidence on the efficacy of avapritinib.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	In line with NICE scope. A patient access scheme has been approved and is included within this submission.	Not applicable.

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If evidence allows subgroup analysis by disease type to include: • aggressive systemic mastocytosis • systemic mastocytosis with associated haematological neoplasm • mast cell leukaemia	Although not a prespecified subgroup analysis, results by disease subtype are presented for the avapritinib studies.	To inform the economic analysis a comparative analysis by disease subtype would be required in treatment-naïve patients (first line of therapy [1L]) and separately in patients who previously received a systemic therapy (2L+). In the key trial underpinning the clinical efficacy of avapritinib (PATHFINDER), patient numbers in the ASM and MCL subtypes treated with avapritinib as a 1L or 2L+ therapy do not reach the minimal requirement to perform any statistical meaningful analysis. Therefore, comparative analyses were not carried out for the disease subtypes by line of therapy. The feasibility of comparing the three AdvSM subtypes in a matching-adjusted indirect comparison (MAIC) was investigated. In addition to the limitations regarding the number of patients available for this analysis, an adjusted comparison was not possible because the baseline characteristics for each subtype were not reported in the comparator evidence.

Special considerations including issues related to equity or equality	No issues relating to equity or equality raised in the scope.	Blueprint Medicines does not believe that the draft remit or scope will exclude people protected by equality legislation. However, it should be noted that, unlike midostaurin, avapritinib does not contain gelatine as an excipient.	Inclusion of gelatine can be problematic for people with certain religious or cultural beliefs, particularly those of the Islamic faith for whom this product may not be considered to be halal. Provision of a gelatine-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.[8]

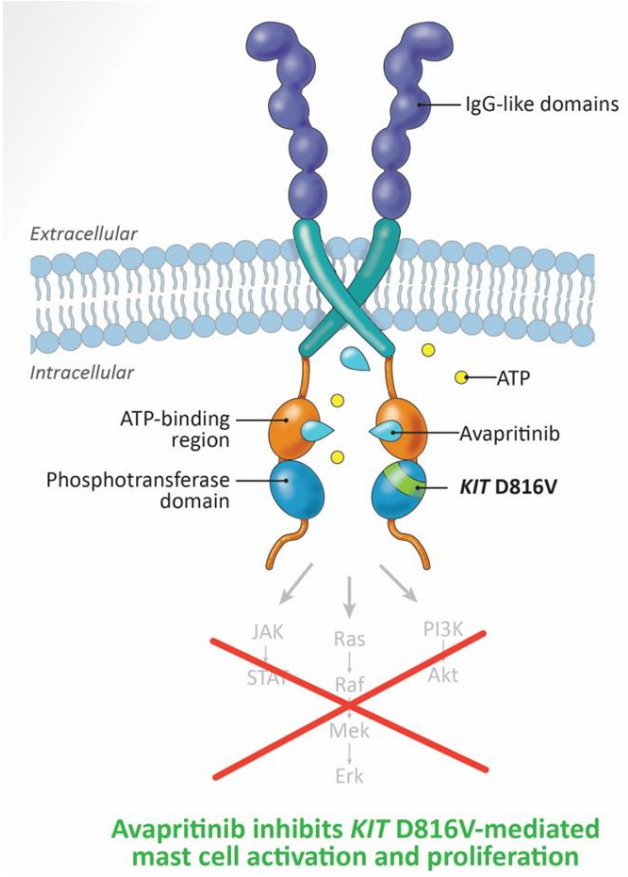
Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BAT, best available therapy; ECS, external control study; HES, hospital episode statistics; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MCL, mast cell leukaemia; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; SM-AHN, systemic mastocytosis with associated haematological neoplasm; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

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

Table 2. Technology being evaluated

UK approved name and brand name	Avapritinib (Ayvakyt®)
Mechanism of action	Avapritinib inhibits the activity of a group of proteins in the body called tyrosine kinases. Mast cells in patients with AdvSM or cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells. Specifically, avapritinib is a type 1 tyrosine kinase inhibitor (TKI) that has demonstrated in vitro activity against the KIT D816V variant protein, which is an underlying driver of systemic mastocytosis (SM) in ~95% of patients.[9-13] Type 1 kinase inhibitors bind and inhibit the active conformation of the kinase receptor (responsible for the majority of AdvSM cases), whereas type 2 inhibitors, such as imatinib, bind to the inactive receptor conformation.[11] Avapritinib has increased potency compared to other TKIs; the half-maximal inhibitory concentration against the KIT D816V protein — where lower concentrations indicate stronger inhibition — of avapritinib is 0.27 nM, which is much less than that of other TKIs such as imatinib (8150 nM) and midostaurin (2.7 nM).[11] With sub-nanomolar potency, avapritinib binds and inhibits the KIT protein while in its active conformation, stopping constitutive receptor activation and therefore halting further downstream signalling pathways that promote mast cell activation.[9,11] Avapritinib specifically targets the ATP-binding site on KIT, preventing the activation of downstream signalling pathways and uncontrolled mast cell activation and proliferation mediated by KIT D816V variant protein-mediated receptor dimerisation (Figure 1).[14]

	Figure 1. Mechanism of action of avapritinib  Source: Gilreath et al. 2019[15]; Evans et al. 2017[11]; Bauer et al. 2021[14]
Marketing authorisation/CE mark status	An application for marketing authorisation for a Type II variation via the national procedure was submitted to the MHRA on [redacted]. Anticipated date of GB marketing authorisation is [redacted]. Avapritinib received EU marketing authorisation in March 2022 as a monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL), after at least one systemic therapy. In the US, avapritinib is approved by the FDA for the treatment of adult patients with AdvSM.[16] In addition, avapritinib received EU marketing authorisation in December 2022 for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.[17]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Avapritinib is anticipated to be indicated for the treatment of [redacted]. In patients with AdvSM, avapritinib is not recommended in patients with platelet counts <50 × 10^9/L.[9]
Method of administration and dosage	The recommended starting dose of avapritinib is 200 mg orally once daily.[9] The dose should be adjusted based on safety and tolerability. The recommended dose reductions are as follows: • first dose reduction 100 mg daily, • second dose reduction 50 mg daily, • third dose reduction 25 mg daily. Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 200 mg to 50 mg orally once daily.[9]
Additional tests or investigations	No additional tests are required for identification of eligible patients. Before initiating avapritinib the risk for intracranial haemorrhage should be carefully considered in patients with risk factors such as; severe thrombocytopenia, vascular aneurysm, history of intracranial haemorrhage within a year, history of cerebrovascular accident or transient ischaemic attack.[9] In patients with AdvSM, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts <50 × 10^9/L.[9]
List price and average cost of a course of treatment	The list price of avapritinib, 25 mg, 50 mg, 100 mg, or 200 mg tablets (30 tablets) is £26,667.[18] The average cost for a course of treatment at PAS price is estimated to be £[redacted].
Patient access scheme (if applicable)	A simple discount PAS has been submitted to NHS England with this initial evidence submission to NICE. This is to ensure enough time for full consideration in advance of the committee meeting. This PAS discount price for avapritinib has been included in the economic analyses in this submission.

Abbreviations: AdvSM, advanced systemic mastocytosis; Akt, protein kinase B; ASM, aggressive systemic mastocytosis; ATP, adenosine triphosphate; EMA, European Medicines Agency; Erk, extracellular signal-regulated kinase; FDA, Food and Drug Administration (US); IgG, immunoglobulin G; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; NHS, National Health Service; PAS, patient access scheme; PASLU, Patient Access Scheme Liaison Unit; PDGFRA, platelet-derived growth factor receptor alpha; PI3K, phosphatidylinositol-3 kinase; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated haematological neoplasm; TKI, tyrosine kinase inhibitor; US, United States

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

B.1.3.1 Health condition

B.1.3.1.1 Summary

- Advanced systemic mastocytosis (AdvSM), is a rare, heterogeneous haematologic neoplasm characterised by hyperactivation and accumulation of mast cells which often leads to severe and debilitating symptoms, life-threatening organ damage, and poor prognosis.[10,11,15,19-22]
- AdvSM encompasses the most severe forms of systemic mastocytosis (SM): ASM, SM-AHN, and MCL. SM-AHN is the most prevalent subtype, accounting for 60–70% of AdvSM cases.[23]
- In approximately 95% of SM cases, disease is driven by a specific mutation (the *KIT* D816V mutation) in the *KIT* gene encoding a receptor tyrosine kinase.[10,11,15,20-22]
- AdvSM is a very rare orphan disease with a low level of prevalence and incidence in Europe based on currently available data. The prevalence of AdvSM in England is estimated to be considerably lower than 1:50,000. Analysis of Hospital Episode Statistics (HES) data in England estimated a prevalence of [redacted] cases of AdvSM per 1 million people in 2022, and an incidence of [redacted] per 1 million people.[24]
- Survival varies from time of diagnosis depending on the disease subtype of AdvSM, that is, 2 months for people with MCL, 3 years for people with SM-AHN and 6 years for people with ASM.[23,25]
- AdvSM can be characterised by severe and often unpredictable symptoms, including gastrointestinal (GI), neurocognitive, and systemic symptoms (such as those related to life-threatening anaphylaxis).[26,27]
- The chronic, severe, and often unpredictable nature of symptoms in AdvSM deeply affects quality of life, including moderate-extreme emotional, psychological and physical disabilities impacting on ability to perform daily work or leisure activities.[27] People with AdvSM frequently need to seek healthcare assistance because of sudden onset of symptoms, including emergency care following the onset of anaphylactic symptoms.[22]

B.1.3.1.2 Disease definition

AdvSM is a debilitating and life-threatening disease that imparts a heavy burden on patients due to the numerous symptoms that can affect multiple different organs.[15,23,25-28] AdvSM

encompasses the most severe forms of SM, which is a rare, heterogeneous disease driven by the activating *KIT* D816V mutation and characterised by an accumulation of neoplastic mast cells in the bone marrow in addition to other organs and tissues.[19]

SM is classified by the World Health Organization (WHO) as a myeloid neoplasm. The minority of patients with SM (~10%, based on the range of estimates in the literature) present with AdvSM;[12,23,29] it represents the most aggressive and life-threatening forms and is divided into ASM, SM-AHN, and MCL. In addition to AdvSM, non-advanced forms of SM also exist, including both indolent SM (ISM) and smouldering SM (SSM).[6,30,31]

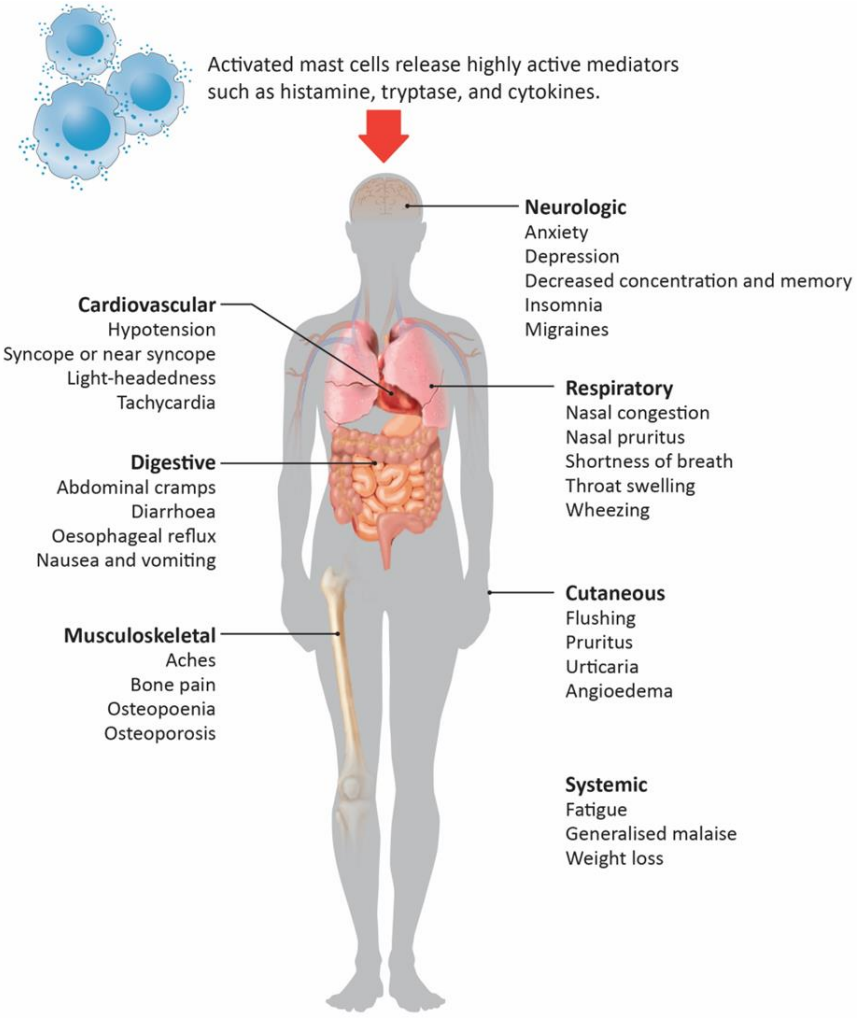
B.1.3.1.3 Aetiology and pathophysiology

The *KIT* gene encodes for the KIT protein (CD117), which is a receptor tyrosine kinase responsible for mast cell proliferation, survival, and activation .[26,32] Mutations to the *KIT* gene are heavily implicated in the aetiology of SM, including AdvSM; the *KIT* D816V mutation is associated with approximately 95% of SM cases.[10,11,15,20-22] The mutation results in constitutive activation of the KIT receptor, triggering signalling pathways that lead to cell proliferation and the accumulation of mast cells in various organs and tissues.[32]

Mast cells are white blood cells that are present throughout the body, where they play an important role in innate and adaptive immune responses in addition to other physiological roles.[33] In SM, abnormal mast cells proliferate in an uncontrolled fashion and infiltrate into various organs and tissues. The presence of increased mast cells and their inflammatory mediators (e.g. histamine, tryptase, prostaglandin D2, and leukotrienes) results in a variety of severe systemic clinical manifestations, including gastrointestinal, musculoskeletal, cardiac and cutaneous issues, neurocognitive effects, and increased risk of anaphylaxis (Figure 2 and 'Symptoms' Section B.1.3.1.5).[6,26-28,34]

Compared to non-advanced SM, in AdvSM the organ infiltration of mast cells is associated with organ damage.[6,26,27]

Figure 2. Clinical manifestations of mast cells and mast cell mediators in AdvSM



AdvSM, advanced systemic mastocytosis. Source: Theoharides et al. 2015[26]; Jennings et al. 2018[27]

B.1.3.1.4 Epidemiology

SM has a prevalence of ~1:10,000 and an incidence of ~1 in 100,000 person per year.[29] The minority of patients with SM (~10%, based on the range of estimates in the literature) present with AdvSM.[12,23,29] In recognition of this rare condition, avapritinib was granted orphan designation by the European Medicines Agency (EMA) for the treatment of mastocytosis.[35]

AdvSM is a very rare group of diseases, occurring almost exclusively in adults, with a low level of prevalence and incidence in Europe based on currently available data. Of patients with AdvSM, ~60–70% of patients have SM-AHN, ~25% have ASM, and ~5–10% have MCL.[23] Of patients with SM-AHN or ASM,16–18% show disease progression to a more advanced form.[23]

In a retrospective cohort study of 548 Danish adults from 1997 to 2010, incidence rates per 100,000 for ASM, SM-AHN, and MCL were estimated to be 0.01, 0.04, and 0.01, respectively.[29] From the same study, prevalence per 100,000 was estimated to be 0.09 for ASM and 0.31 for SM-AHN, while the prevalence of MCL was estimated to be zero, based on the low number of patients with MCL identified (5 out of 548 patients).[29] A German study of 140 patients identified incidence and prevalence rates for AdvSM of 0.08 and 0.52 per 100,000, respectively.[36] This study also provided some evidence to suggest that AdvSM predominantly arises in males, with a male to female ratio of 2:1 and found the median age at diagnosis to be 68,[36] similar to findings in the Danish study.[29] A lower age of diagnosis has been reported in patients in the ECNM registry (median 62 years) and a retrospective study of UK patients (median 65 years).[23,37] In addition, a clinical expert in the UK stated that the median age of diagnosis of AdvSM in clinical practice in the UK was earlier, and similar to that reported for patients with SM (median 52 years of age).[38] Estimates of European prevalence from Orphanet are 0.1–0.9/100,000 for ASM, 1–9/100,000 for SM-AHN, and <0.1/100,000 for MCL.[39-41]

The epidemiology of AdvSM in England is poorly described. To inform estimates of incidence and prevalence, an analysis of HES datasets was carried out. In this descriptive retrospective cohort study, national, patient-level, HES data for England was used to investigate the epidemiology, management and health care resource utilisation (HCRU) for AdvSM patients in England.[24] Prevalence and incidence were estimated based on ICD-10 codes and included patients aged 18 years or older at the time of their AdvSM recorded diagnosis in HES, between 1 April 2018 and 31 March 2023. Incident AdvSM patients were only included in the cohort if they were aged 18 years or older at the time of their first AdvSM recorded diagnosis in HES between 1 April 2019 to the 31 March 2023, and had no prior record of AdvSM before the start of the study period.[24]

The HES analysis reported a prevalence of [redacted] cases of AdvSM per 1 million people in 2022. Prevalence appears to be increasing over time, from [redacted] per 1 million people in 2018.[24] Incidence of AdvSM in England was [redacted] per 1 million people in 2022,[24] which equates to [redacted] new cases of AdvSM in England per annum.

The HES figures are in alignment with those provided during the midostaurin assessment in 2020 [TA728], where it was reported that approximately 40 new patients are diagnosed with AdvSM in the UK each year, of which 34 patients are estimated to be diagnosed annually with AdvSM in England.[42]

B.1.3.1.5 Symptoms

Many debilitating symptoms are associated with SM, and these are also present and often worse in AdvSM. The infiltration and activation of mast cells in different organ systems leads to many different types of symptoms, including headache, brain fog/cognitive issues, depression, fatigue, diarrhoea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux, bone pain, flushing, rash, and pruritis (Figure 2).[6,22,43,44] Patients with AdvSM have described uncontrollable diarrhoea, which prevents them from leaving the

confines of their home, and intense muscle and joint pain, which affects their ability to perform physical tasks.[43] AdvSM also predisposes patients to severe life-threatening anaphylaxis.[45,46]

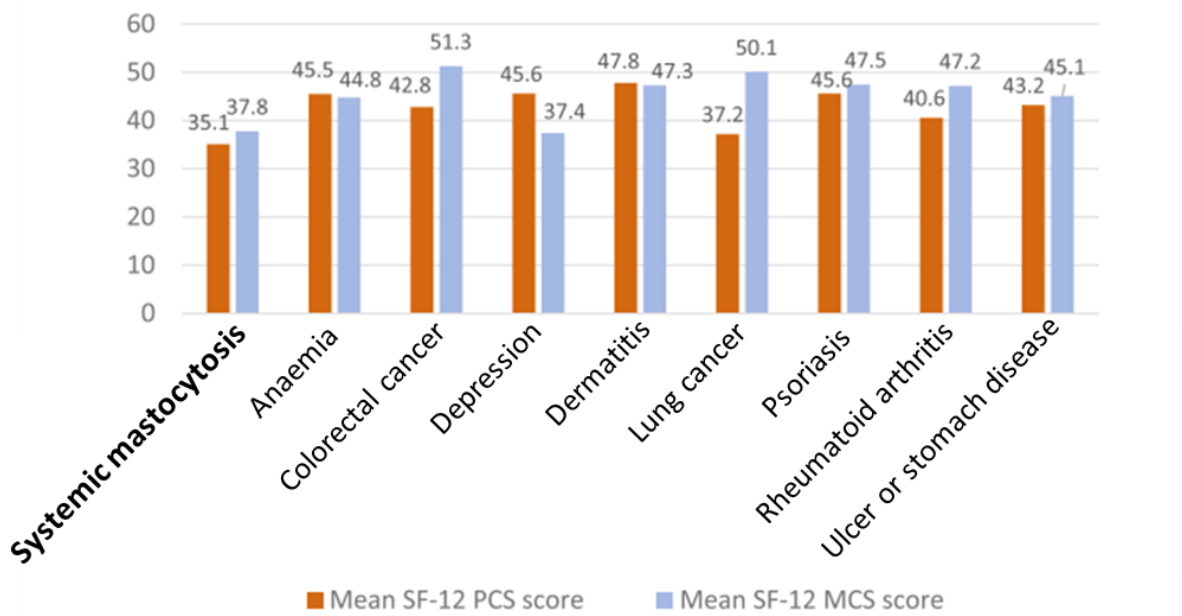
There are many different symptom triggers (i.e., events that lead to mast cell activation) that are difficult for patients to avoid. For example, triggers include hot or cold temperatures, stress, fatigue, certain foods and beverages, insect bites, odours, infections, medications, and exercise.[26,27] The TouchStone Survey is a real-world study in SM that captured patient perspectives on the holistic impact of disease and assessed HRQoL and the impact of SM on daily activities, work impairment, and health care use in US adults with a self-reported SM diagnosis.[22] Results of the survey, that included 56 patients with SM (5/56 [9%] patients had ASM and 1/56 [2%] had SM-AHN), revealed that patients experience an average of 14 symptoms related to SM over their lifetime.[22]

In addition to experiencing symptoms associated with mast cell burden in tissues, patients with AdvSM also experience cancer-related symptoms such as weight loss, cytopenia, organomegaly and ascites.[45]

B.1.3.1.6 Health-related quality of life and patient perspective

Patient's health-related quality of life (HRQoL) is affected by SM and its advanced forms. In the TouchStone survey, the mental component score (MCS) and physical component score (PCS) of the SF-12 score in patients with SM were shown to be lower (indicating lower HRQoL) than those in many other conditions with high disease burden, with MCS most comparable to patients with depression and PCS most comparable to patients with lung cancer (Figure 3).[22] These comparisons suggest that the impact of SM on patients' HRQoL is severe. It should also be noted that in the TouchStone survey, only 9% of patients had ASM and 2% had SM-AHN.[22] Due to the greater severity of disease in all forms of AdvSM, it could be expected that HRQoL would be worse if examined specifically in this patient population. In addition to dealing with symptoms of disease, patients with SM have also reported feelings of alienation and marginalisation in relationships with healthcare professionals (HCPs).[45] The Perceptions, Realities and Insights on Systemic Mastocytosis (PRISM) survey has examined the experiences of advanced and non-advanced SM patients, as well as gaining perspectives from healthcare providers treating SM in seven countries in Europe (UK, France, Switzerland, Spain, Italy, Austria and Germany).[47] In PRISM, UK participants with AdvSM (n=19) reported decrements in physical and mental health decrements on the SF-12 (PCS: 37.6, MCS: 41.4) and EQ-5D (mean index score: 0.630). Additionally, in the PATHFINDER trial of avapritinib, patients with AdvSM at baseline (before treatment) demonstrated poor HRQoL via a mean score of only 37.8 points (standard deviation [SD]: 24.2) on the European Organisation for Research and Treatment of Cancer Quality of Life 30-Item Core Questionnaire (EORTC QLQ-C30; range 0–100, where 0 represents the lowest quality of life [QoL]).[48]

Figure 3. SF-12 mental and physical component scores in SM



MCS, mental component score; PCS, physical component score; SF-12, 12-item Short Form survey; SM, systemic mastocytosis. Note: Lower scores indicate worse HRQoL. Source: Mesa et al.[22]

Patients with AdvSM are burdened with a high number of HCP consultations over a yearly period. This includes appointments with primary care physicians, allergists, immunologists, gastroenterologists, dermatologists, and oncologists.[22] Due to the debilitating symptoms and frequent need to seek healthcare, patients with AdvSM suffer from losses in work-related productivity.[22,45] In the TouchStone survey, work impairment in patients with SM was quantified and results were stratified by epinephrine use and severe pain.[22] Approximately 54% of patients with SM reported reducing work hours and 27% quit their job because of SM. The study also revealed that the symptom of severe pain was more associated with work impairment compared to using injectable epinephrine.[22] In the PRISM survey, 74% (n=14) of UK patients with AdvSM reported that SM impacted their work in one or more ways (including reduced hours, medical disability, and termination). In addition, patients with AdvSM reported missing 8.6 hours of work due to SM in the week before the survey.[47]

B.1.3.1.7 Mortality

Unlike the non-advanced forms of SM, AdvSM is a fatal disease.[25] Poor survival estimates have been associated with all forms of AdvSM (Table 3). Specifically, MCL is associated with the shortest life expectancy while ASM has been demonstrated to be associated with the longest life expectancy from diagnosis, albeit only approximately 5 years. In a retrospective study of 342 patients with SM (183 with AdvSM) seen at the Mayo Clinic between 1976 and 2007, median survival times from diagnosis of 3.4 years, 2 years, and 2 months were observed in patients with ASM, SM-AHN, and MCL, respectively.[25] In a separate analysis of patients with AdvSM spanning between 1978 and 2017, data from the Data Registry of the European Competence Network on Mastocytosis (ECNM) and the

Spanish Association of Mastocytosis (Red Española de Mastocitosis; REMA) indicated median survival times from diagnosis of 5.7 years, 2.9 years, 1.9 years for patients with ASM, SM-AHN, and MCL, respectively.[23] This study also identified 10-year overall survival rates of 44%, 11.2%, and 29.9% for patients with ASM, SM-AHN, and MCL and determined that in 109 (75%) of the 145 patients with AdvSM that died, the cause of death was related to mastocytosis.[23] Patients live in fear due to shortened life expectancy, and the emotional burden of living with the uncertainty of survival has been demonstrated in patients with AdvSM.[45]

Table 3. Median overall survival in AdvSM

AdvSM subtype	Lim et al. 2009[25]		Sperr at al. 2019[23]	
	Patients	Median OS	Patients	Median OS (95% CI)
ASM	41	3.4 years	62	5.7 years (0.6, 4.5)
SM-AHN	138	2 years	174	2.9 years (2.5, 3.3)
MCL	4	2 months	23	1.9 years (0, 5.2)

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, confidence interval; MCL, mast cell leukaemia; OS, overall survival; SM-AHN, systemic mastocytosis with associated haematologic neoplasm.

B.1.3.2 Clinical pathway of care

B.1.3.2.1 Summary

- The management of patients with AdvSM in the UK largely occurs in six key specialist centres, including one recognised Centre of Excellence (Guy's and St Thomas' NHS Foundation Trust, London).
- There are currently no UK-specific guidelines for the management of patients with AdvSM, however the National Comprehensive Cancer Network (NCCN) and ECNM have published guidance of the diagnosis and management of patients with SM and mast cell disorders, including AdvSM.
- The diagnosis of AdvSM and its subtypes is complex. A diagnosis of AdvSM is dependent on a diagnosis of SM, which has been defined by criteria set by the WHO (2023 classification) and by the International Consensus Criteria [ICC].[49-51] If the criteria for the diagnosis of SM are met, separate criteria exist to differentiate all three forms of AdvSM.
- The goals of therapeutic management in patients with AdvSM include the reduction of the potentially severe and often unpredictable symptom burden, reduction of mast cell burden, and prolonging survival.[43]
- In the UK, midostaurin is the only therapy indicated for use in patients with AdvSM, including all three forms of the disease: ASM, SM-AHN and MCL, and is recommended by NICE in this indication.[42]
- Off-label therapies considered for use in patients with AdvSM include: cladribine,

imatinib, and pegylated interferon alpha. Due to lesser efficacy or issues with safety, these are included in the US NCCN guidelines as “other recommended regimens”.[5] Clinical experts in England stated that cladribine is mainly used as a second- or further-line (2L+) treatment option for AdvSM where midostaurin fails or is not tolerated. It is also considered for patients with high-bulk disease, or for those who are otherwise ineligible to receive midostaurin.

- Imatinib is a TKI; however, it lacks efficacy against *KIT* D816V,[6,15,31] and is generally only considered in patients who do not have the *KIT* D816V variant (only 2-3% of patients).[15]
- Interferon alfa has limited efficacy in the treatment of AdvSM, it is associated with numerous adverse events,[18,19] and is no longer considered a treatment option, whilst the use of pegylated interferon in the UK is minimal.[2,3]
- When available, avapritinib is expected to become a treatment option in all eligible patients with AdvSM and mainly as the first line of treatment. Avapritinib has demonstrated ten-fold greater in vitro activity against *KIT* D816V compared to midostaurin,[11] in addition to demonstrating superior efficacy in patients with AdvSM via indirect treatment comparisons.[7,52,53]

B.1.3.2.2 UK specialist centres

Significant clinical experience with AdvSM in the UK is largely limited to six key specialist centres (Guy's and St Thomas' NHS Foundation Trust, London; University College London Hospitals NHS Foundation Trust, Royal Liverpool University Hospital, Oxford University Hospital, Beatson West of Scotland Cancer Centre Glasgow, and Cardiff University Hospital). Guy’s and St Thomas’ NHS Foundation Trust is an established Centre of Excellence, in association with the ECNM, and as such is a major referral site able to guarantee optimal state-of-the-art diagnosis, management, and therapy of patients with all types of MC disorders, including mastocytosis and its variants.[54]

B.1.3.2.3 Diagnosis

The diagnosis of AdvSM and its subtypes is dependent on a diagnosis of SM. Criteria for the diagnosis of SM, as defined by the WHO and refined by the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias (ICC), are shown in Table 4. Diagnosis of SM is made when one major and one minor criterion are both met, or when three or more minor criteria are met.[49-51]

Table 4. Criteria for diagnosis of SM

Major criterion
• Multifocal dense infiltrates of tryptase- and/or CD117-positive MCs (≥15 MCs in aggregates) in sections of BM and/or other extracutaneous organ(s).
Minor criteria

- In biopsy sections of BM or other extracutaneous organs, >25% of all MCs in the infiltrate are spindle-shaped or have atypical morphology; or, of all MCs in BM aspirate smears, >25% are immature or atypical.
- *KIT* point mutation at codon 816 or in other critical regions of *KIT* in BM, blood, or another extracutaneous organ.
- MCs in BM, blood, or another extracutaneous organ express CD25, CD2, and/or CD30 in addition to normal MC markers.
- Baseline serum tryptase concentration >20 ng/mL (in the case of SM-AHN, this is not valid as an SM minor criterion).

BM, bone marrow; CD, cluster of differentiation; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MC, mast cell; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated haematologic neoplasm.
Source: Valent et al. 2021[55]; Khoury et al. 2022[49]; Arber et al. 2022[50]

Diagnosis of the specific variants of SM requires assessment of clinicopathologic features described as B- or C-findings, with B-findings indicating overall burden of mast cells and expansion of the neoplastic process into various organs with no obvious impairments of organ function, including signs of dysplasia or myeloproliferation or organomegaly, while C-findings indicate organ damage and dysfunction due to mast cell infiltration.[56] A flow chart summary of the diagnosis of SM, including all forms of AdvSM, is provided in Figure 4.

If the criteria for the diagnosis of SM are met, separate criteria exist to differentiate all three forms of AdvSM:

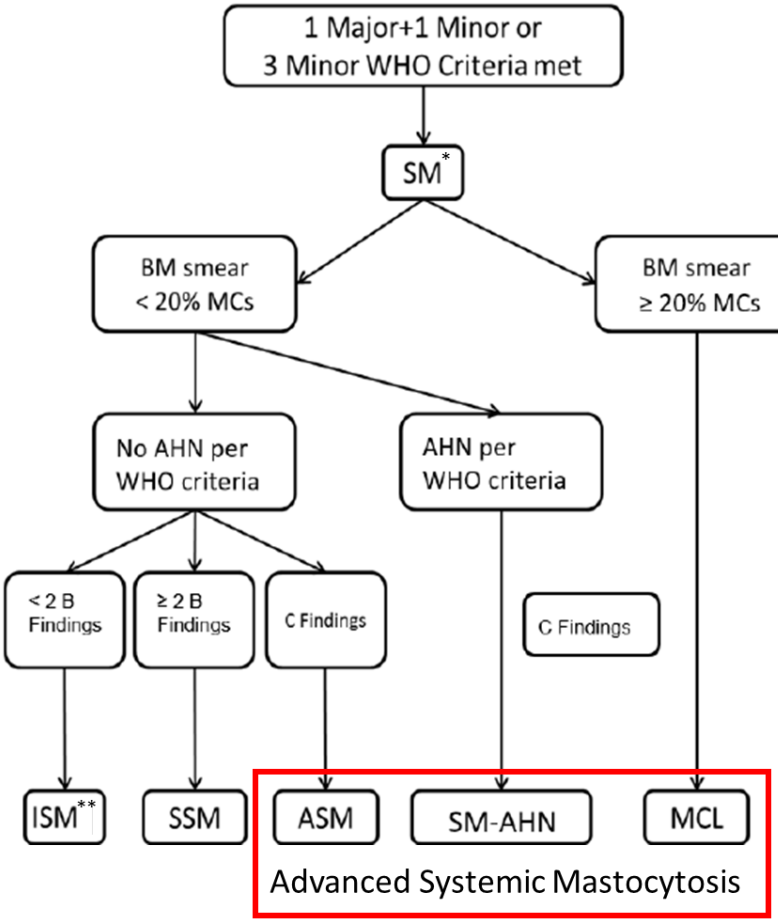
- Diagnosis of ASM is dependent on identification of one or more clinical findings known as C-findings, which indicate organ damage from the infiltration of mast cells.[30,55,57,58]
- Diagnosis of SM-AHN depends on the diagnosis of SM, in addition to also meeting the WHO criteria for an AHN.[57] A number of associated neoplasms have been identified in patients with SM-AHN, including neoplasms of myeloid origin, lymphoma, myeloma, and chronic lymphocytic leukaemia.[6,25] Patients with SM-AHN can also present C-findings.
- MCL is differentiated from SM by further increased levels of mast cell infiltration in the bone marrow. Specifically, the diagnosis of MCL is made when the proportion of mast cells in bone marrow aspirate is demonstrated to be 20% or greater. Patients with MCL can also present C-findings.

Clinical experts in the UK advised that the diagnosis of AdvSM and its subtypes is complex.[3] When a patient is referred to an expert centre, experts will look to confirm the diagnosis of AdvSM and identify the presence or absence of AHN (~70% of patients with AdvSM have the SM-AHN subtype). As part of the patient evaluation, patients will undergo a diagnostic assessment, which includes bone marrow biopsy, serum tryptase levels and *KIT* gene mutation analysis amongst other tests, to confirm the AdvSM diagnosis. In addition, the mutational profile of the disease, including the *KIT* gene, may be analysed at the point of referral, and patients classified according to prognostic groups using the Mutation-Adjusted

Risk Score (MARS) and the International Prognostic Scoring System in Mastocytosis (IPSM).[3]

If the presence of an AHN is confirmed, the expert will evaluate the SM and AHN components of the disease to establish whether the SM component or the AHN component requires priority treatment. This step is important as both components require different treatments to reduce the disease burden and prolong survival.[3]

Figure 4. Diagnosis flow chart of AdvSM



AdvSM, advanced systemic mastocytosis; AHN, associated haematologic neoplasm; ASM, aggressive systemic mastocytosis; BM, bone marrow; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukaemia; SM, systemic mastocytosis; SSM, smouldering systemic mastocytosis; WDSM, well-differentiated systemic mastocytosis; WHO, World Health Organization. *WDSM can occur in any subtype of SM. **BM mastocytosis is a variant of ISM characterised by a lack of skin lesions and no C- or B-findings. Note: B-findings represent a set of criteria that indicate high mast cell burden without evidence of organ damage and C-findings represent a set of criteria that indicate organ damage from mast cell infiltration. Source: Valent et al. 2007[57]; Pardanani 2019[57]; Khoury et al. 2022[49]; Arber at al. 2022[50]

B.1.3.2.4 Treatment guidelines

Although in development, there are currently no UK guidelines for the management of patients with AdvSM.[3]

In 2022, a “User’s Guide for Daily Clinical Practice” was published in a joint effort from the ECNM and the American Initiative in Mast Cell Diseases (AIM).[59] The publication provides a review of multidisciplinary aspects in diagnosis and patient-specific management and a guide for application of markers, algorithms, prognostic scores, and treatments for use in daily practice.

The US NCCN published a 2022 update for the treatment of SM.[5] The NCCN guide includes detailed treatment pathways for ASM, SM-AHN, and MCL, in addition to stepwise prophylactic approaches for the treatment of common symptoms of SM. The approaches to symptom treatment and use of disease-modifying treatments aligns with published clinical expert recommendations.[57]

B.1.3.2.5 Treatment of symptoms

The treatment of symptoms should be considered in all patients with AdvSM.[5,57] NCCN and ECNM guidelines provide recommendations for the prevention and treatment of anaphylaxis, which is a severe and common side effect of AdvSM.[5,59] This includes the use of antihistamines (H1 and H2 blockers) and epinephrine, complemented by IV fluids, oxygen, corticosteroids and bradykinin inhibitors. For the involvement of organ systems and associated symptoms in AdvSM, a stepwise approach for prophylactic therapies is presented in the 2022 NCCN and joint ECNM-AIM guidelines.[5,59]

B.1.3.2.6 Therapeutic management

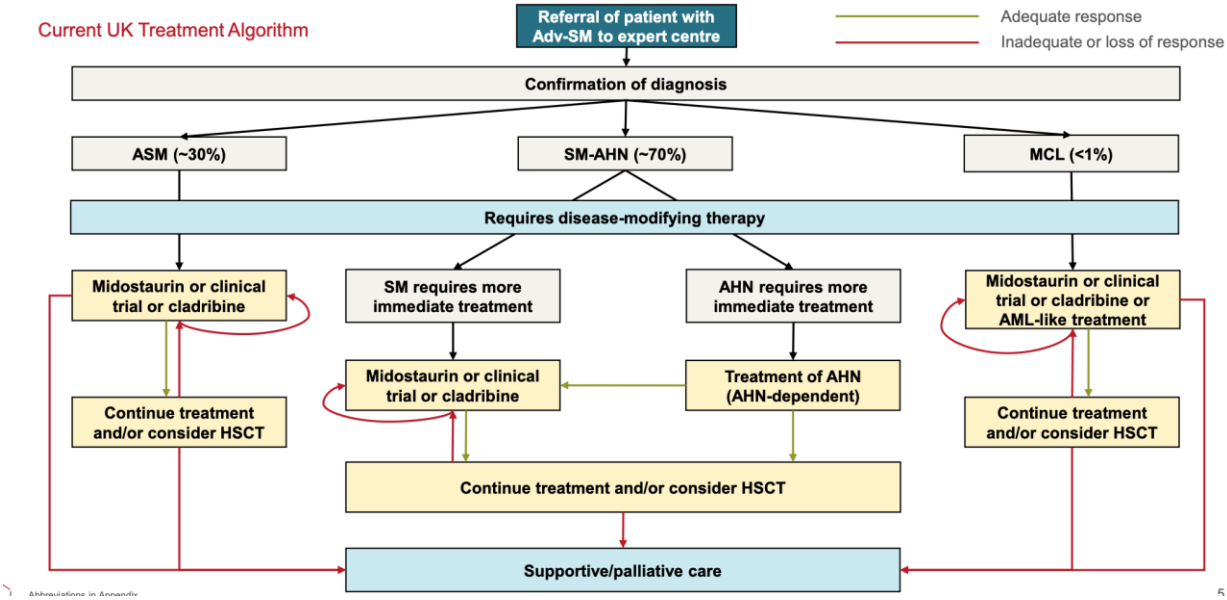
In AdvSM, the treatment objectives are to prolong survival, rapidly reduce mast cell burden, and improve the symptom burden.[43] The complexity of managing the heterogeneous clinical manifestations of varying severity necessitate a multidisciplinary team and a personalised management approach.[44]

Traditional treatment options range from observation alone (supplemented by preventative measures to avoid precipitating symptoms of mast cell mediator release) to symptom management (such as pruritus or diarrhoea), supportive measures (such as red blood cell transfusion or osteoporosis treatment), or cytoreductive therapy for mast cell debulking in the setting of AdvSM. Allogeneic haematopoietic stem cell transplant (allo-HSCT) is another treatment modality that can prolong overall survival (OS) and progression-free survival (PFS) in select patients with AdvSM.[44]

B.1.3.2.6.1 Disease-modifying therapies

The current treatment pathway for AdvSM in the UK, based on expert advice from five consultant haematologists in the UK, is shown in Figure 5.[2,3]

Figure 5. Current treatment pathway for AdvSM in the UK



Abbreviations: AdvSM, advanced systemic mastocytosis; AHN, associated haematological neoplasm; ASM, aggressive systemic mastocytosis; HSCT, haematopoietic stem cell transplant; MCL, mast cell leukaemia, SM, systemic mastocytosis.

Source: Cogentia. UK Expert Validation, 2022 [data on file][3]; MAP Patient Access. UK Primary research report, 2023 [data on file][2]

In the UK, midostaurin is the only therapy specifically indicated for use in patients with AdvSM, including all three forms of the disease: ASM, SM-AHN, and MCL, and currently is the only NICE-recommended treatment for AdvSM.[42] Midostaurin was the first approved therapy for AdvSM, receiving market authorisation from the EMA on 18 September 2017.[60] Midostaurin is an inhibitor of multiple tyrosine kinases.[60] While midostaurin has demonstrated activity against KIT D816V in vitro, this activity has been shown to be approximately 10 times lower compared to avapritinib.[11] In a Phase 2 open-label study of midostaurin in patients with AdvSM, the reported overall response rate (ORR) was 60%; however, this assessment was based on the Valent criteria,[61] which do not require full resolution of C-findings (C-findings define the presence of debilitating organ damage), in addition to presenting other drawbacks in assessing treatment response.[62] Post hoc analyses using the International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria demonstrated a 28% ORR, with complete remission (CR) in less than 1% of patients.[60]

All patients with AdvSM in the UK are likely to be offered midostaurin as a first-line (1L) treatment option when the SM component of the disease is advancing or is more aggressive (excluding Scotland, where it is not recommended for routine reimbursement due to the absence of a submission from the holder of the marketing authorisation).[2,3] Midostaurin, and other disease-modifying treatment options, are not required in patients who have low-risk AHN (SM-AHN patients). These patients will continue to be monitored closely by clinicians and only receive supportive treatment until the SM and/or AHN component of the disease becomes more aggressive and requires treatment.[3] In analysis of HES data (1 April 2018 to

31 March 2023), midostaurin use was observed amongst [redacted] patients) of the incident cohort post-diagnosis.[24]

Off-label therapies considered for use in patients with AdvSM include cladribine, imatinib, and pegylated interferon alpha. Due to lesser efficacy or issues with safety, these are included in the NCCN guidelines as "other recommended regimens".[5] These therapies include tyrosine kinase inhibitor (TKIs) and treatments with other mechanisms of actions.

Cladribine is a chemotherapeutic agent sometimes used to target mast cells. Cladribine has shown some efficacy against SM but is associated with adverse events (AEs) including neutropenia and lymphopenia, resulting in immunosuppression and opportunistic infection.[6,15,31] Clinical experts in England stated that cladribine is mainly used as a second-line (2L) treatment option for AdvSM where midostaurin fails or is not tolerated. It is also considered for patients with high-bulk disease, or for those who are otherwise ineligible to receive midostaurin. In this limited cohort, it is given for a short period of 1-2 courses, before introducing a disease-modifying agent for deeper responses. Regardless of treatment line, cladribine is considered in a very limited number of cases (approximately 5% of patients).[38]

Imatinib is a TKI; however, it lacks efficacy against KIT D816V,[6,15,31] which is the driver of the disease and present in approximately 95% of SM cases.[10,11,15,20-22] For this reason, the off-label use of imatinib is only considered in the small number of patients (2-3%) who do not have the *KIT* D816V variant.[5,15] Similar to imatinib, dasatinib and nilotinib are TKIs and have shown low response rates when tested in patients with AdvSM.[15] Clinical experts advised that imatinib may be considered as a third-line (3L) treatment option in AdvSM, but that neither dasatinib nor nilotinib are used in current clinical practice in England.[2] In the analysis of HES data (1 April 2018 to 31 March 2023), other than midostaurin, [redacted] for the treatment of AdvSM, including imatinib, was identified.[24] In a real-world study that collected data on treatment of patients with AdvSM in Europe and the US between 2009 and 2011, less than 1% of known lines of therapy were with imatinib.[7]

Interferon alpha has also shown activity against mast cells, although responses are delayed and relapse is common after treatment cessation, highlighting that interferon alpha stops mast cell replication, but may not kill mast cells.[6] Additionally, interferon alpha is associated with numerous AEs, including flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism.[6,31] Pegylated interferon may be used for AdvSM patients with bone disease and problems with osteoporosis and osteopenia, or in progressive disease after all other therapies have been tried. Only 4% of known lines of therapy in the real-world study were with pegylated interferon alpha) and is use in the UK for AdvSM is minimal.[3,7,63]

When the AHN component of the disease is more aggressive or has a high risk of progression, the treatment of AHN is prioritised over treatment of the SM component. The treatment provided is dependent on the type of AHN present:[3]

- Azacytidine can be used to treat patients with high-risk chronic myelomonocytic (CMML) (CMML1 or CMML2) or myelodysplastic syndrome (MDS).
- Decitabine can be used to treat patients with high-risk CMML (CMML1 or CMML2) or

MDS.

- Ruxolitinib can be used to treat patients with myelofibrosis (MF) or myeloproliferative neoplasm (MPN).
- Hydroxycarbamide can be used to treat patients with MPN.

Once the AHN is in a state of remission, disease-modifying treatment may be introduced to treat the SM component of the disease.

B.1.3.2.6.2 HSCT

Allo-HSCT can be a curative therapy for AdvSM, as progenitor cells in the bone marrow that carry pathogenic mutations can be replaced with transplanted tissue. In a retrospective assessment of patients with AdvSM, including patients with ASM (N=7), SM-AHN (N=38), and MCL (N=12), responses were observed in 70% of patients (28% CR) after allo-HSCT, although responses were not assessed via the IWG-MRT-ECNM or modified IWG-MRT-ECNM (mIWG-MRT-ECNM) criteria.[64] Please see Appendix M, Section M1 for an exploration of the mIWG-MRT-ECNM response criteria. Additionally, three-year OS of 57% was observed, with the lowest rates in patients with ASM (43%) and MCL (17%).[64] It is important to note that the median age of patients in the study was 46, which is younger than the typically observed age of diagnosis of AdvSM, of approximately 65 to 70.[29,36]

The presence of numerous eligibility criteria restricts allo-HSCT to approximately 10% of AdvSM patients in the UK.[3] According to clinicians, advanced age (above 65 years of age) and low levels of fitness are significant deterrers when determining whether to refer patients for allo-HSCT.[3,65] Additionally, allo-HSCT requires a donor, which requires compatibility between patient and donor human leukocyte antigen (HLA) expression,[66] or transplant rejection-related reactions can occur. In 2016, an expert consensus on allo-HSCT in AdvSM was published, stating that allo-HSCT should only be considered in patients under the age of 60 who have a complete HLA-matched sibling donor or an unrelated donor with no comorbidities.[67] Therefore, allo-HSCT is only suitable for a limited subset of patients with AdvSM.[67] Of note however, eligibility for and subsequent efficacy of allo-HSCT is enhanced in patients that demonstrate remission in their condition after receiving therapy (see section B.1.3.3 below).[3]

B.1.3.3 Unmet need in treatment of AdvSM

AdvSM is a debilitating and life-threatening disease.[23,25] In addition to shortened survival, the burden of disease is also very high from the patient perspective due to the numerous symptoms that can affect multiple different organs.[15,26-28] AdvSM also severely impacts patients' HRQoL, demonstrated by patient-reported outcome measures that suggest comparability to depression and lung cancer.[22] Additionally, health-cost resource use in patients with AdvSM is heavily increased compared to patients without SM or AdvSM, leading to elevated costs to healthcare systems.[68]

Treatment protocols for AdvSM have previously focused on treating symptoms and employing off-label therapies with poor efficacy and safety profiles.[28] Midostaurin is a TKI with EMA market authorisation for the treatment of patients with AdvSM,[1] and currently is the only NICE-recommended treatment for AdvSM in the UK. While midostaurin has demonstrated activity against KIT D816V in vitro, this activity has been shown to be approximately 10 times lower compared to avapritinib.[11] Additionally, when using more effective novel tools to assess the efficacy of midostaurin in patients with AdvSM, response to therapy and complete remission are rare. In patients with AdvSM, ORRs of 60% and 69% have been reported following midostaurin treatment, as assessed by the modified Valent criteria, with no complete remissions after 12 treatment cycles (48 weeks).[69] In a post hoc analysis, midostaurin had an ORR of 28% as assessed by the more stringent IWG-MRT-ECNM criteria (see Appendix M, Section M1 for a description of the AdvSM response criteria).[60,70] Of note, regarding midostaurin, the ECNM guidelines stated:[71] "*However, only a few patients enter complete remissions and the number of patients with advanced SM who relapse under treatment with midostaurin is relatively high*."

In PATHFINDER, an ORR of 74%, evaluated by mIWG-MRT-ENCM criteria, was observed with avapritibinib treatment, with complete remission or complete remission with partial hematologic recovery in 27% (median follow-up of 26 months).[72,73] There is consensus from clinical experts in the UK that the better the response of an AdvSM patient to disease-modifying treatment pre-HSCT, the better the prognosis of the patient post-HSCT.[3] Three patients with AdvSM in the UK, two of whom participated in the EXPLORER trial and one who received treatment on a named-patient basis, achieved complete remission (CR) after avapritinib treatment and have been successfully bridged to allo-HSCT.[74] This demonstrates the efficacy of avapritinib, and suggests that when combined with allo-HSCT, a curative option is available for patients with AdvSM.

In indirect treatment comparisons (ITCs), superior results for avapritinib have been demonstrated when considering OS, ORR, and CR in patients with AdvSM (Section B.2.9).[52,53]

Midostaurin is associated with gastrointestinal AEs and requires a twice-daily dosing regemin.[1] In the pivotal Phase 2 trial of midostaurin in patients with AdvSM, 72% of patients discontinued treatment, including 33% due to disease progression and 22% due to AEs.[69]

Other than avapritinib, no other therapies directly target the underlying or genetic cause of disease. Selective targeting of KIT D816V is expected to offer impactful clinical benefits for all patients with AdvSM by targeting an underlying driver of the disease in 95% of patients,[9-13] thereby overcoming the shortcomings of current management options.

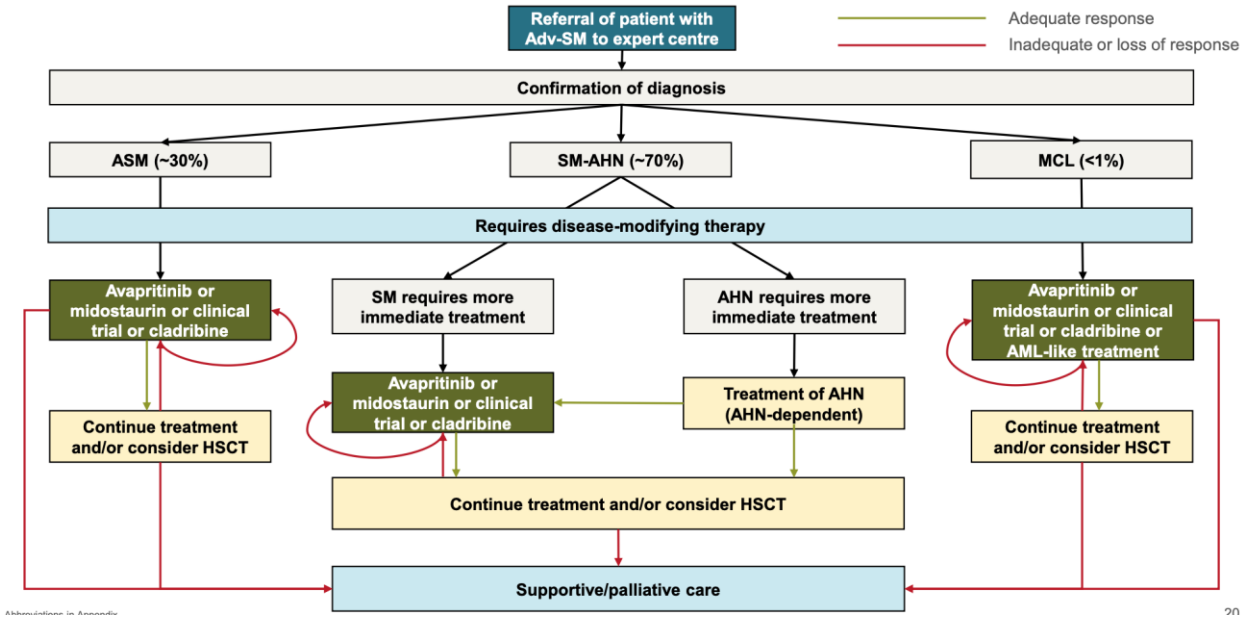
B.1.3.4 Position of avapritinib in the treatment pathway

The general consensus amongst five expert consultant haematologists in the UK is that, should a broad indication for AdvSM be achieved, avapritinib would be used mainly as a 1L treatment option, in patients that require treatment of the SM component (Figure 6).

Clinicians stated that except where contraindicated, avapritinib would be considered before midostaurin in the treatment pathway, due to demonstrated superiority vs. best available therapy (BAT) in external control studies, increased potency and an improved tolerability profile vs. midostaurin.[2,3] Clinical experts stated that avapritinib would be particularly useful in patients with gastrointestinal (GI) issues and those being considered for allo-HSCT, while patients who are at particularly high risk of bleeding e.g. those on high dose anticoagulants/dual antiplatelet agents, or have low platelet levels (avapritinib is not recommended in people with platelets <50 x 10^9/L) may be considered for midostaurin first.[2,3]

The ECNM and NCCN recommend avapritinib, alongside midostaurin, as a treatment for AdvSM, with the ECNM noting that it may be especially effective in eradicating most or all neoplastic (*KIT* p.D816V+) MCs.[5,59] The recommendation reflects the efficacy of avapritinib across all AdvSM subtypes and regardless of treatment line demonstrated in uncontrolled studies and the superior outcomes observed in indirect treatment comparisons against other available therapies.[7,48,52,73,75-77]

Figure 6. Position of avapritinib in the treatment pathway for AdvSM in the UK



Abbreviations: AdvSM, advanced systemic mastocytosis; AHN, associated haematological neoplasm; ASM, aggressive systemic mastocytosis; HSCT, haematopoietic stem cell transplant (allogeneic); MCL, mast cell leukaemia, SM, systemic mastocytosis.

Source: Cogentia. UK Expert Validation, 2022 [data on file][3]; MAP Patient Access. UK Primary research report, 2023 [data on file][2]

B.1.4 Equality considerations

Blueprint Medicines does not believe that the draft remit or scope will exclude people protected by equality legislation. However, it should be noted that, unlike midostaurin, avapritinib does not contain gelatine as an excipient. Inclusion of gelatine can be problematic for people with certain religious or cultural beliefs, particularly those of the Islamic faith for

whom this product may not be Halal. Provision of a gelatine-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.[8]

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify the efficacy, safety, and tolerability of treatment options used in patients with AdvSM (see Appendix D). The SLR included all approved or investigational pharmacological interventions used for the treatment of AdvSM, including ASM, SM-AHN and MCL, however this submission will focus on evidence related to the intervention (avapritinib) and the comparators listed in the decision problem, that is, midostaurin, cladribine, imatinib and interferon alpha.

Systematic database searches were performed on 22nd June 2023 and updated on 7th November 2023. A total of 79 publications were included in the review, of these 72 were identified in the initial review and 7 in the update. As some studies were associated with multiple publications, secondary publications were combined. Hence, the evidence comprised 32 non-randomised controlled trials (RCTs)/observations studies from 79 publications, but no RCTs. Of the 32 studies, 30 were identified in the initial review and 2 in the update.

Across both reviews there were no RCTs reporting data for people with AdvSM that met the eligibility criteria for the review.

Of the 32 included studies (not mutually exclusive):

- 4 studies reported evidence for avapritinib
- 16 studies reported evidence for midostaurin
- 8 studies reported evidence for cladribine
- 1 study reported evidence for imatinib
- 2 studies reported evidence for interferon alpha (not specified as pegylated interferon)

The remaining studies (n=5) included only a mixed intervention such as ‘cytoreductive therapy’ or comparators outside the scope of this submission.

A full list of the 32 included studies in shown in Appendix D, Table 9.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Avapritinib studies and comparative analyses

The efficacy and safety of avapritinib has been demonstrated in the pivotal Phase 2 trial PATHFINDER, an ongoing open-label, single-arm study (starting dose of 200 mg administered orally every day [OD]) in patients with AdvSM.[48,72]

Data from the Phase 1 dose-finding study, EXPLORER, in which a smaller number of patients (20 out of 69) received the starting dose of 200 mg OD, provide supportive evidence with longer-term follow-up (a median follow-up of 45 months).

EXPLORER is a Phase 1 dose-finding study that included starting doses of avapritinib of 30 mg to 400 mg once daily (OD); only a small number of patients (20 out of 69) received the starting dose of 200 mg OD. Data from EXPLORER provide supportive evidence with longer-term follow-up (a median follow-up of 45 months).[75,76] An overview of the EXPLORER study is provided in Table 5, however since the individual study results do inform the economic analysis the study is described further in Appendix M, Sections M2 and M3.

Since PATHFINDER and EXPLORER are single-arm studies, an external control study ([ECS] BLU-285-2405) was conducted to provide comparative data against therapies used in clinical practice. In this study, real-world retrospective data on best available therapy (BAT) used to treat patients with AdvSM was generated and used in comparative analyses of efficacy and safety against patients treated with avapritinib (in clinical studies).[7,53] Further comparative data are available from an MAIC that assessed outcomes in patients treated with avapritinib and midostaurin in clinical studies (Section B.2.9.3).[52]

The trials are summarised in Table 5 and an overview of the available data cut-offs for PATHFINDER and EXPLORER is shown in Table 6. In all clinical trials where avapritinib has been assessed, a daily oral dosing regimen has been used.

The economic model incorporates data from the pivotal PATHFINDER study and comparative data from the ECS. PATHFINDER is the key avapritinib study informing the economic model and is described in Sections B2.3–B2.7.

Pooled analyses of EXPLORER and PATHFINDER have been used in indirect comparisons (Section 2.9). However, due to sufficient data being available from the pivotal Phase 2 PATHFINDER study (September 2022 data cut-off), updated comparative analyses of the external control study include PATHFINDER alone (Section B.2.9.2) and are used to inform the economic model.

Table 5. Clinical effectiveness evidence for avapritinib

Study	**EXPLORER (BLU-285-2101; NCT02561988)**	**PATHFINDER (BLU-285-2202; NCT03580655)**	**External Control Study (BLU-285-2405; NCT04695431)**
Primary study reference	DeAngelo et al., 2021[75]	Gotlib et al., 2021[48]	Reiter et al., 2022[7]

Study	EXPLORER (BLU-285-2101; NCT02561988)	PATHFINDER (BLU-285-2202; NCT03580655)	External Control Study (BLU-285-2405; NCT04695431)
Additional study publications/ sources	Deininger et al., 2018,[78] Gotlib et al., 2020,[79] Radia et al., 2021,[80] DeAngelo et al., 2017,[81] Drummond et al., 2017,[82] Taylor et al., 2021,[83] Gotlib et al., 2020,[84] Vannucchi et al., 2020,[85] DeAngelo et al., 2022,[76] Reiter et al., 2022[86] Radia et al., 2022[87]	Maurer et al., 2021,[88] Maurer et al., 2021,[89] Radia et al., 2023,[90] DeAngelo et al., 2021,[91] Reiter et al., 2021,[92] Radia et al., 2022,[93] Reiter et al., 2022,[86] Radia et al., 2022[87] Gotlib et al., 2023[73]	Reiter et al., 2022,[94] Reiter et al., 2022,[77] Reiter et al., 2022,[95] Gotlib et al., 2022,[96] Reiter et al., 2022[53]
Unpublished sources	EXPLORER CSR, 2020,[97] EXPLORER SAP, 2020,[98] Summary of Clinical Efficacy 2.7.3,[99] Summary of Clinical Safety 2.7.4[100]; EXPLORER FINAL CSR, 2024[101]	PATHFINDER CSR, 2020,[102] PATHFINDER SAP, 2020,[103] Summary of Clinical Efficacy 2.7.3,[99] Summary of Clinical Safety 2.7.4,[100] PATHFINDER Clinical Summary (2022 data cut-off)[72]	BLU-285-2405 CSR, 2021,[104] BLU-285-2405 Study Protocol, 2021,[105] 2021; ECS analysis vs. 1L midostaurin (data on file),[106] ECS analysis vs. 2L+ BAT (data on file),[107] ECS analysis vs. 2L+ cladribine (data on file)[108]
Study design	Phase 1, international, multicentre, open-label, dose-finding and expansion study	Phase 2, international, multicentre, open-label, single-arm study	Multicentre, observational, retrospective chart review study
Population	Adults with AdvSM and other myeloid malignancies (N=86, AdvSM n=69, other n=17)	Adults with AdvSM (N=107)	Adults with AdvSM (n=141 [analytical cohort])
Intervention(s)	Avapritinib, once daily • Part 1: starting doses of 30 mg to 400 mg • Part 2: starting doses of 200 mg or 300 mg	Avapritinib, starting dose of 200 mg once daily	Non-interventional study. In the observational retrospective real-world cohort patients received BAT, including midostaurin and cladribine. For the comparative analyses, patients treated with avapritinib in EXPLORER and PATHFINDER were included.

Study	EXPLORER (BLU-285-2101; NCT02561988)	PATHFINDER (BLU-285-2202; NCT03580655)	External Control Study (BLU-285-2405; NCT04695431)
Comparator(s)	None	None	Not applicable (see above)
Indicate if study supports application for marketing authorisation	Yes	Yes	No
Indicate if study used in the economic model	Yes - Data from EXPLORER are not used in the base-case economic analysis, but are included in the MAIC that is used to inform a scenario analysis regarding eligibility for allo-HSCT.	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable	Not applicable
Reported outcomes specified in the decision problem [outcomes in bold are incorporated into the model]	• OS • PFS • **Response rate*** • Adverse effects of treatment • HRQoL	• **OS** • **PFS** • **Response rate*** • Symptom severity • **Adverse effects of treatment** • **HRQoL**	• **OS**
All other reported outcomes **[outcomes in bold are incorporated into the model]**	• Measures of mast cell burden • DOR • TTR	• Measures of mast cell burden • DOR • TTR	• **DOT****

*Response rate in EXPLORER and PATHFINDER is used in the matching-adjusted indirect comparison that informs eligibility for allo-HSCT in a model scenario analysis.

**DOT from the ECS is used in a model scenario analysis

Abbreviations: 1L, first line of therapy; 2L+ second or later line of therapy; AdvSM, advanced systemic mastocytosis; BAT, best available therapy, CSR, clinical study report; DOR, duration of response; DOT, duration of treatment; ECS, external control study; HRQoL, health-related quality of life; HSCT, haemopoietic stem cell transplantation; MAIC, matching-adjusted indirect comparisons; OS, overall survival; PFS, progression-free survival; SAP, statistical analysis plan; TTR, time to response

Table 6. Avapritinib study data cut-offs and key data sources

Data cut-off	EXPLORER (BLU 285-2101)	PATHFINDER (BLU 285-2202)
Registrational (USPI)	**27 May 2020** DeAngelo et al., 2021[75]; EXPLORER CSR, 2020 [data on file][97] Data not presented.	**23 June 2020** (prespecified interim analysis) Gotlib et al., 2021[48];PATHFINDER CSR, 2020 [data on file][102] Presented in Appendix M, Section M4*
EU D120 (SmPC)/ MHRA	**21 April 2021** MHRA Summary of Clinical Efficacy 2.7.3, Blueprint Medicines [data on file][99] Data not presented. [Pooled efficacy analysis shown in Appendix M, Section M5, pooled safety analysis shown in Appendix M, Section M6.]	**20 April 2021** MHRA Summary of Clinical Efficacy 2.7.3, Blueprint Medicines [data on file][99] Presented in Appendix M, Section M4* [Pooled efficacy analysis shown in Appendix M, Section M5, pooled safety analysis shown in Appendix M, Section M6.]
In 2022	**05 April 2022** DeAngelo et al., 2022[76] Results presented in Appendix M, Section M3.	**09 September 2022** Gotlib et al., 2023[73]; PATHFINDER Clinical Summary (2022 data cut-off)[72] Results presented in ○ Section B.2.6.1 (200 mg starting dose) – **key submission data used in economic model** ○ Appendix M, Section M4*
In 2023	**19 January 2023** (database locked 10 April 2023; final results are now available) EXPLORER CSR, 2023 [data on file][97] Data not presented.	**September 2023** (results expected to be available Q2 2024) Data not available.

*In addition to patients who received a starting dose of 200 mg OD (n=105), this analysis includes two patients who received a starting dose of 100 mg OD

Additional supportive evidence is available from a matching-adjusted indirect comparison (MAIC) in which individual patient data from the two avapritinib studies were indirectly compared with aggregate data from two Phase 2 studies evaluating midostaurin in people with AdvSM (D2201and A2213).[52] The MAIC provides comparative evidence for ORR, in addition to OS and CR, and informs a scenario analysis in the economic model exploring the

impact of avapritinib on eligibility for allo-HSCT. The MAIC is described in detail in Section B.2.9.3.

The clinical experience of 13 patients with AdvSM who have received avapritinib at 11 centres in the UK via an open-label compassionate use program (CUP) is also reported in this submission.[109] Due to the small patient numbers, this data was not used to populate the economic model but is described in Section B.2.6.3. The results from this small cohort of patients reflect the clinical heterogeneity of AdvSM and provides real-world evidence (RWE) in the UK that mirrors the PATHFINDER trial outcomes.

B.2.2.2 Clinical effectiveness evidence for comparator therapies

An overview of the comparator studies identified in the SLR is shown in Appendix D, Table 9. Except for four single-arm studies (the two midostaurin studies included in the MAIC,[69,110] one study investigating cladribine study[111] and one study investigating interferon alpha[112]), studies of midostaurin, cladribine, imatinib or interferon alpha were retrospective, observational studies. Other than the midostaurin studies included in the MAIC, these studies do not inform the current evidence submission and are not described in further detail.

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

B.2.3.1 Study design and endpoints

See Appendix M, Section M1 for a detailed description of outcomes measures used in AdvSM, including assessment of response by mIWG-MRT-ECNM criteria and patient-reported outcome measures.

B.2.3.1.1 EXPLORER

EXPLORER is an open-label Phase 1 study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with AdvSM and relapsed or refractory myeloid malignancies.[97,113] This two-part study included dose escalation (Part 1) and expansion (Part 2) to further evaluate safety and tolerability, and to assess the clinical efficacy of avapritinib at the maximum tolerable dose (MTD)/recommended Phase 2 dose (RP2D). Further details on the methodology of EXPLORER are described in Appendix M, Section M2.

B.2.3.1.2 PATHFINDER

PATHFINDER is an ongoing open-label, single-arm Phase 2 study evaluating the safety and efficacy of avapritinib (starting dose of 200 mg administered orally every day) in patients with AdvSM (Table 7).[102,114] In contrast to EXPLORER, in which a local diagnosis of AdvSM was used for eligibility, a central diagnosis and evaluable C-findings at baseline were prospectively established by the central pathologist and a study steering committee (SSC) chair (or designee) during screening, prior to enrolment).[102]

Patients with a centrally confirmed WHO diagnosis of AdvSM were enrolled into one of two cohorts (planned enrolment N=103, Figure 7):[102]

- Cohort 1: AdvSM patients with ≥1 mIWG-MRT-ECNM criteria for evaluable disease (have an evaluable C-finding or have MCL) as determined by the SSC
- Cohort 2: AdvSM patients who were not considered eligible for an adjudicated mIWG-MRT-ECNM response as determined by the SSC

It should be noted that, with the exceptions of study sites in Germany, midostaurin-naïve patients were eligible for the study based on encouraging results from EXPLORER where the majority of patients were midostaurin-naïve as EXPLORER was initiated before the approval of midostaurin.[102]

B.2.3.1.2.1 Endpoints

Patients in Cohort 1 support the primary objective of determining SSC adjudicated ORR by mIWG-MRT-ECNM criteria. Both cohorts are included in the analyses of secondary and exploratory efficacy objectives (listed in Table 7). The key secondary endpoint was the mean change from baseline in AdvSM-SAF total symptom score (TSS) (see Appendix M, Section M1). Other secondary endpoints included time to event outcomes (TTR, duration of response [DOR], PFS, and OS) and further analyses of response rates.[102]

Like other studies in AdvSM, central adjudication of C-findings was performed by an SSC, equivalent to the RAC of the EXPLORER study, for more uniformity in this complex assessment. Central pathological review of bone marrow samples, central radiology reads of spleen assessments and central laboratory measurement of serum tryptase assessments were implemented to ensure consistency across this multicentre study.[102]

B.2.3.1.2.2 Protocol amendments

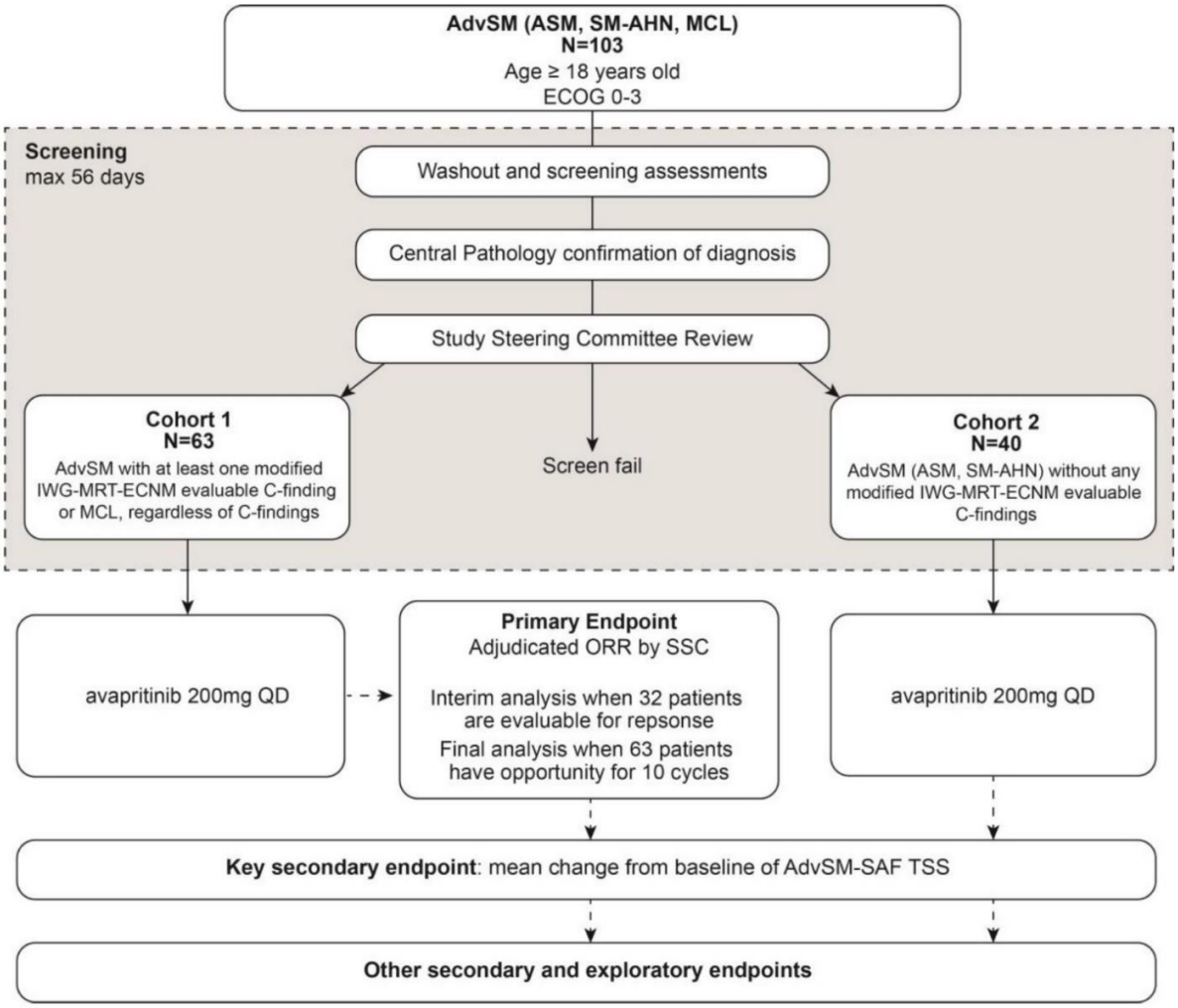
Ten amendments to the original protocol (09 January 2018) were issued in total. Key amendments are as follows (Full details on the major protocol modifications see Table 3, PATHFINDER CSR):[102]

Important amendment changes were as follows:

- Changes to dosing:
  - With Protocol Amendment 1, the starting dose was reduced from 300 mg OD to 200 mg OD based on findings from EXPLORER.

    - With Protocol Amendment 3, a 100 mg OD starting dose was permitted for patients with platelet counts from 25,000 to 50,000/µL at baseline.
    - No patient was enrolled under the initial protocol and received a starting dose of 300 mg OD. Two patients received a starting dose of 100 mg OD, and all other patients received a starting dose of 200 mg OD.
    - With Protocol Amendment 1, dosing guidelines were updated to include information regarding dose reduction in the event of toxicity, with the lowest permitted dose being 50 mg OD; this was further reduced to 25 mg OD under Protocol Amendment 3.
- Further major changes with Protocol Amendment 3 also allowed enrolment of patients with AdvSM who were lacking evaluable C-findings at baseline (Cohort 2), which was considered appropriate given the rarity of the disease, high unmet medical need, and the need for additional safety and efficacy data. These patients contribute to powering the key secondary endpoint of patient-reported outcomes using the AdvSM-SAF, local efficacy assessments, safety, and other secondary and exploratory endpoints.
- Under Protocol Amendment 5, further measures to reduce the incidence of patients experiencing severe thrombocytopenia were introduced, including the exclusion of patients with platelet counts <50,000/µL at baseline.
- Under Protocol Amendment 7, patients who experienced intracranial bleeding had to permanently discontinue treatment.

Figure 7. Study Schematic of PATHFINDER



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; max, maximum; MCL, mast cell leukaemia; ORR, overall response rate; OD, once daily; SAF, Symptom Assessment Form; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; SSC, Study Steering Committee; TSS, total symptom score.

Source: PATHFINDER CSR, Blueprint Medicines, 2020 [data on file][102]

B.2.3.1.3 External control study

The external control arm study aimed to generate real-world data on BAT used to treat patients with AdvSM, and to conduct comparative analyses of efficacy and safety outcomes between patients treated with avapritinib in the EXPLORER and the PATHFINDER vs. BAT in clinical practice.[104]

To generate real-world data on BAT, a multicentre, observational, retrospective chart review study was conducted. Longitudinal, individual-level data were collected using medical chart abstraction among eligible patients with AdvSM who received systemic treatment at participating study sites in Europe and the US. Study sites were selected based on their

status as centres of excellence for the treatment of AdvSM (Table 7). De-identified patient data were abstracted from medical records into a standardised eCRF from March 26, 2021, to October 4, 2021.[104]

Baseline demographic, treatment history, and clinical information was assessed prior to or on each index date (i.e., during the baseline period). Follow-up (i.e., observation period) spanned from the index date until either the latest available data in patients' charts; initiation of avapritinib (i.e., for external control patients who went on to enrol in the EXPLORER or PATHFINDER trials or received avapritinib through the CUP); diagnosis of a new primary malignancy other than AdvSM; or death.[104]

Real-world patients with AdvSM were identified using inclusion and exclusion criteria based on those of the EXPLORER and PATHFINDER trials (Table 7). Due to the rarity of the disease and the extensive list of eligibility criteria of the EXPLORER and PATHFINDER trials, it was not feasible to apply all trial eligibility criteria to the external control population. However, certain eligibility criteria were defined to ensure that the external control patients were similar to the trial patients with respect to important disease characteristics. Patients who received BAT as 1L treatment and received avapritinib as 2L+ as part of the EXPLORER and PATHFINDER trials or the CUP were included in the external control arm to minimise the possibility of selection bias. Given that patients who are not eligible for the EXPLORER and PATHFINDER trials are likely to be clinically different from those who are eligible for the trials (e.g., contraindications to treatment, potentially sicker than included patients), it was important to include these patients in the external control arm to help facilitate comparable cohorts. For these patients, their follow-up period was censored at avapritinib initiation.[104]

After patient selection, critical imbalances across the external control patients and trial patients were adjusted for using analytical techniques (see Section B.2.9.2).[104]

External control patients may have initiated treatment with different lines of treatment (LOTs) at the study sites. For example, some patients may have initiated 1L treatment at a study site while other patients may have received second or later lines of therapy ("2L+ cohort") at a study site, having received 1L therapy elsewhere. Patients were not required to initiate 1L therapy at a study site to be eligible for this study. Where data on multiple lines therapy were available for a single eligible patient, information for all lines was collected, and all LOTs were included in this analysis. The index date was defined as the date of initiation of each line of systemic therapy at a participating site (Figure 8).[104]

B.2.3.1.3.1 Endpoints

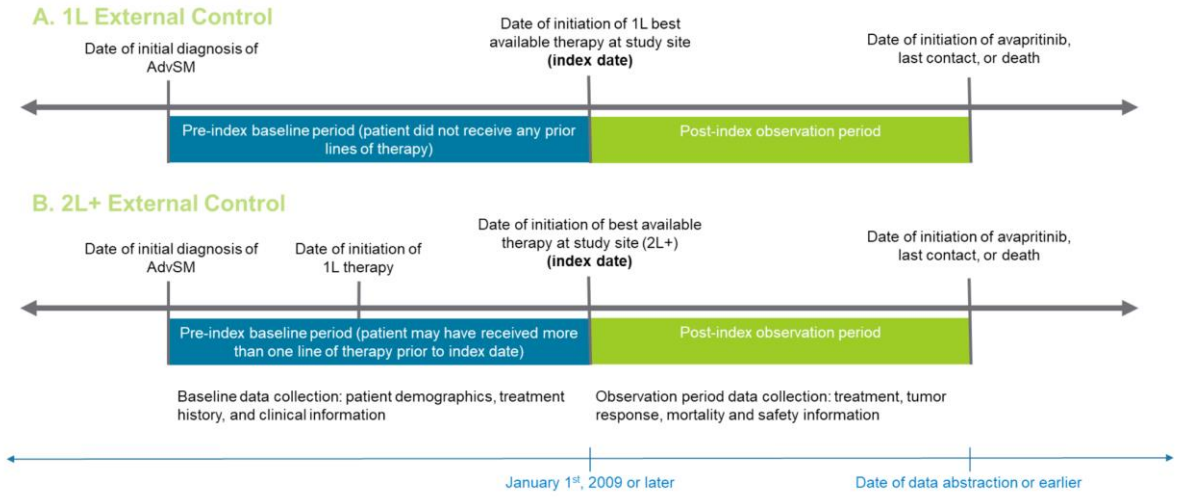
The study aimed to conduct an indirect cross-study comparison between patients treated with avapritinib in the EXPLORER and PATHFINDER trials and real-world patients treated with BAT, for the primary endpoint of OS, as well as secondary endpoints of duration of treatment (DOT) and maximum and two-month reduction in serum tryptase from baseline.[104]

B.2.3.1.3.2 Protocol amendments

The original protocol (version 1.0) was dated December 12, 2020. There was one amendment to the original protocol (to create protocol version 2.0), which was dated July 15, 2021. Protocol version 2.0 updated the original protocol in the following ways:[104]

- Updated inclusion criteria to remove the requirement of having available performance status, and updated exclusion criteria on history of another primary malignancy to be consistent with the exclusion criteria used in the EXPLORER and PATHFINDER trials.
- Updated secondary endpoint change in serum tryptase from baseline to the end of treatment to be change in serum tryptase from baseline to a specified timepoint, and maximum reduction in serum tryptase during a LOT for sections related to endpoints, comparative analysis, and limitations.
- Updated language on ORR to pure pathological response rate in sections related to exploratory objective, statistical hypothesis, study population, endpoints, comparative analysis, and limitations.

Figure 8. External Control Study – Study Design



Abbreviations: 1L+, first line of therapy, 2L+, second line or later line of therapy, AdvSM, advanced systemic mastocytosis.

Source: External Control Study (BLU-285-2405) CSR, Blueprint Medicines, 2021 [data on file][104]

Table 7. Comparative summary of trial methodology

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]
Trial design	Phase 2, international, multicentre, open-label, single-arm study	International, multicentre, observational, retrospective chart review study

Eligibility criteria for participants (Key Inclusion)	• Adult ≥18 years of age
	• One of the following diagnoses, confirmed by WHO diagnostic criteria:
	  ○ ASM
	  ○ SM-AHN. The AHN must be myeloid, with the following exceptions that are excluded: AML, myelodysplastic syndrome that is very high- or high-risk, a myeloid AHN ≥10% BM or PB blasts, Philadelphia chromosome-positive malignancies. Incidental indolent, low-grade lymphoid AHNs (e.g., chronic lymphocytic leukaemia) not requiring treatment are eligible.
	  ○ MCL, including diagnoses with an AHN component.
	• Patients with SM-AHN should have received prior treatment for the AHN component of disease if, in the opinion of the Investigator, such therapy was appropriate.
	• Patient must have a BM biopsy taken within 56 days of C1D1, assessed by the Central Pathology Laboratory.
	• Cohort 1 only: Patient must have at least one of the specified measurable C-findings, per modified IWG-MRT-ECNM criteria, attributed to SM
	• Serum tryptase ≥20 ng/mL
		• Adult (≥18 years of age) at the initiation of first systemic line of therapy at the participating site, which must be on or after January 1, 2009
		• Diagnosed with AdvSM, with known disease subtype including SM-AHN, ASM, or MCL
		• Received at least one line of systemic therapy for AdvSM, which may include but not limited to regimens containing:
		  ○ Multikinase inhibitor: Midostaurin
		  ○ Cytoreductive therapy: cladribine, interferon alpha, azacitidine, decitabine
		  ○ Selective TKI: imatinib, nilotinib, dasatinib
		  ○ Hydroxyurea
		  ○ Antibody-drug conjugates: brentuximab vedotin, gemtuzumab ozogamicin
		• Had an index date at least 3 months prior to the start of data collection (in order to include patients with at least 3 months of follow-up after index date), unless the patient died within three months from index date

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]
	• Patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance • Patient's non-antineoplastic SM therapies must be stable • ECOG performance status of 0 to 3	

Eligibility criteria for participants (Key Exclusion)	• Prior treatment with avapritinib
	• Prior cytoreductive therapy or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy less than 28 days before obtaining screening BM biopsy
	• Prior radiotherapy within 14 days before the screening BM biopsy
	• Haematopoietic growth factor within 14 days of screening BM biopsy
	• Patients who required therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4
	• Major surgical procedure within 14 days of the first dose of study drug
	• Candidate for allogeneic haematopoietic stem cell transplantation for treatment of SM, in the opinion of the Investigator
	• Eosinophilia and known positivity for the FIP1L1-PGDFRA fusion, unless the patient had demonstrated relapse or PD on prior imatinib therapy
		• Malignancy that was not in remission at time of SM diagnosis, or new non-haematological malignancy diagnosed after SM diagnosis, except for: completely resected basal cell and squamous cell skin cancer, curatively treated localised prostate cancer, and completely resected carcinoma in situ of any site
		• Among patients with SM-AHN, those in whom any of the following was true:
		  ○ the SM component was consistent with ISM or SSM, or
		  ○ the AHN component was a lymphoid malignancy, or one of the following myeloid malignancies: AML, MDS that is very high- or high risk as defined by the IPSS-R, or a Philadelphia chromosome positive malignancy, or

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]

	• History of another primary malignancy diagnosed or required therapy within 3 years before the first dose of study drug
	• Any of the following laboratory criteria:
	  ○ ALT and AST >3.0 × ULN; no restriction if due to suspected liver infiltration by MCs
	  ○ Total bilirubin >1.5 × ULN; no restriction if liver infiltration by the disease being treated or in the presence of Gilbert's Disease. In the case of Gilbert's disease, a direct bilirubin >2.0 ULN was an exclusion
	  ○ Estimated glomerular filtration rate <30 mL/min/1.73 m^2 or creatinine> 1.5 × ULN
	  ○ Platelet count <50,000/μL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s)
	• History of a cerebrovascular accident or transient ischaemic attacks within 1 year before the first dose of study drug
	• Known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding
		○ there was a known FIP1L1/PDGFRA fusion gene (including those with CHIC-2 deletion and partial deletion of PDGFRA), independent of *KIT* mutational status (Patients with known FIP1L1/PDGFRA fusion gene (including those with CHIC-2 deletion and partial deletion of PDGFRA), independent of *KIT* mutational status, were excluded because they typically have SM associated with a hypereosinophilic syndrome or chronic eosinophilic leukaemia, and show a 100% rate of complete response to imatinib, and thus their inclusion may bias the results of this study.
		• Received avapritinib as the first line of systemic therapy for AdvSM at participating site, or prior to initiation of first systemic therapy at participating site.

Settings and locations where the data were collected	International study conducted at sites across North America and Europe. 18 sites enrolled patients and entered data for this CSR, including one site in the UK (Guy's and St Thomas' NHS Foundation Trust, London; nine patients).	Centres of excellence for the treatment of AdvSM: Guy's and St Thomas' NHS Foundation Trust (UK), Hospital Virgen del Valle (Spain), Medical University of Vienna (Austria), and Universitätsmedizin Mannheim (Germany); and Dana Farber Cancer Institute and Stanford Cancer Center in the US. Nine patients in the UK were enrolled in the study.

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]
Trial drugs Intervention(s) (n=[x]) and comparator(s) (n=[x])	Avapritinib, starting dose of 200 mg once daily (N=107)	Best available therapy (n=141 [analytical cohort])
Permitted and disallowed concomitant medication	During the study, strong CYP3A4 and strong or moderate CYP3A4 inducers were prohibited as well as any antineoplastic treatment other than avapritinib (excluding local radiotherapy to treat localised bone lesions). Palliative and supportive care for disease-related symptoms were permitted during the study.	Not applicable.

Primary outcomes (including scoring methods and timings of assessments)	• Adjudicated ORR (CR+CRh+PR+CI) based on mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort 1 only.
	• The ORR is tested for superiority vs. midostaurin (see statistical methods).
		• OS
		  ○ Defined for the BAT cohort as the interval of time between initiation of each eligible line of systemic treatment and death due to any cause).
		  ○ Defined for the avapritinib cohort as the interval of time between the first dose of avapritinib and death due to any cause.

Other outcomes used in the economic model/specified in the scope	• OS
	• PFS
	• Symptom assessment: AdvSM-SAF TSS (key secondary)
	• Time to response and duration of response
	• HRQoL assessments (change from baseline)
	  ○ EORTC QLQ-C30
	  ○ PGIS scale
		• DOT
		• Safety (AEs were only described for the BAT cohort; due to differences in definitions and data collection requirements between of AEs in EXPLORER/PATHFINDER clinical studies and routine clinical practice no comparison with avapritinib was performed).

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]

Further secondary and exploratory outcomes	• Further analyses of response rate were completed but not reported in this submission:
	  ○ Investigator-assessed ORR
	  ○ Objective response rate (CR+CRh+PR) based on PPR criteria
	  ○ CR+CRh+PR and clinical benefit (CR+CRh+PR+CI+SD) based on mIWG-MRT-ECNM criteria
	• Change in mast cell burden
	  ○ Change from baseline in BM mast cells
	  ○ Change from baseline in serum tryptase
	  ○ Change from baseline in *KIT* D816V VAF
	  ○ Change from baseline in spleen and liver volume
	• Pharmacokinetics
		• Change in serum tryptase concentration (change from baseline to a fixed timepoint, of approximately 2 months; maximum on-treatment reduction)
		• Time to next treatment line (TtNTL)

Safety outcomes	Incidence of AEs	AEs that resulted in treatment modification or discontinuation, hospitalisation, or death
Pre-planned subgroups	Analyses of ORR were performed for the subgroups of age (<65 years, ≥65 years), sex (male, female), region (North America, Europe), baseline S/A/R genotype (with, without mutation, prior treatment with midostaurin (yes, no), and prior systemic therapy (yes, no) in RE population. Analyses of DOR and PFS were performed for the subgroups of baseline S/A/R genotype, prior treatment with midostaurin, and prior systemic therapy in RE population. Analysis of OS was performed in the safety population and for the same subgroups listed for DOR and PFS.	The following subgroup analyses were conducted for primary endpoint, OS, and the secondary endpoint, DOT, compared to midostaurin and cladribine (2021and 2022 data cut-off analysis): • Patients who received 1L avapritinib in EXPLORER and PATHFINDER vs. 1L midostaurin patients • Patients who received 1L avapritinib in EXPLORER and PATHFINDER vs. 1L BAT (excluding midostaurin) • Patients who received 2L+ avapritinib in EXPLORER and PATHFINDER vs. 2L+ cladribine patients

Trial number (acronym)	PATHFINDER (BLU-285-2202; NCT03580655)[73,102,115]	External Control Study (BLU-285-2405; NCT04695431)[7,104]
	Disease subtype was not a prespecified subgroup analysis - the study data was to be summarised descriptively by disease subtype	• Patients who received 2L+ avapritinib in EXPLORER and PATHFINDER vs. 2L+ BAT (including midostaurin) • The following subgroup analyses were conducted for primary endpoint, OS compared to BAT (2021 data cut-off analysis)[7,104]: • Patients who received 1L avapritinib in EXPLORER and PATHFINDER, and external controls who received 1L systemic therapy • Patients who received 2L+ avapritinib at 200 mg starting dose in EXPLORER and PATHFINDER, and all external controls who received at least one prior systemic therapy • Patients who received 2L+ avapritinib at 200 mg starting dose or less in EXPLORER and PATHFINDER, and all external controls who received at least one prior systemic therapy • Patients who started avapritinib at 200 mg starting dose or less in EXPLORER and PATHFINDER, and all external controls
Duration of follow-up / loss to follow-up / cross over	As of the September 2022 data cut-off, median follow-up was 26 months. [redacted] patients had been lost to follow-up.	Data were collected between January 1, 2009, and October 4, 2021.

Abbreviations: 1L, first line of therapy, 2L+, second line or later line of therapy; AE, adverse event; AdvSM, advanced systemic mastocytosis; AdvSM-SAF, advanced systemic mastocytosis symptom assessment form; AHN, associated haematological neoplasm; ALT, alanine aminotransferase; AML, acute myeloid leukaemia; AST, aspartate aminotransferase; ASM, aggressive systemic mastocytosis; BAT, best available therapy; BM, bone marrow; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; CSR, clinical study report; DOR, duration of response; DOT, duration of treatment; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life 30-Item Core Questionnaire; HRQoL, health-related quality of life; IPSS-R, Revised International Prognostic Scoring System; ISM, indolent systemic mastocytosis; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; MDS, Myelodysplastic syndrome; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis MTD, maximum tolerable dose; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PGIS, Patient Global Impression

of Symptom Severity; PPR; pure pathological response; PR, partial remission; SAE, serious adverse event; S/A/R, SRSF2, ASXL1 or RUNX1 genes; SM, systemic mastocytosis; SSM, smouldering systemic mastocytosis; SM-AHN, systemic mastocytosis with associated haematological neoplasm; RAC-RE, Response Assessment Committee Response-Evaluable; RP2D, recommended phase 2 dose; TSS, total symptom score; TtNTL, time to next treatment line; ULN, upper limit of normal; VAF, variant allele fraction.
Source: Clinicaltrials.gov[113]; Clinicaltrials.gov[114]; EXPLORER CSR, Blueprint Medicines, 2020;[97] PATHFINDER CSR, Blueprint Medicines, 2020;[102] External Control Study CSR, Blueprint Medicines, 2021;[104] MHRA Clinical Summary 2.7.3, Blueprint Medicines, 2021;[99] EMA, CHMP Assessment Report, 2022[116]

B.2.3.2 Baseline Characteristics

A summary of baseline characteristics for patients treated with 200 mg starting dose of avapritinib in PATHFINDER is provided in Table 8. Baseline characteristics in patients who received avapritinib as a 1L therapy and patients who received avapritinib after one or more prior systemic therapies (2L+) (defined as prior antineoplastic therapies in the per pre-specified subgroup analysis for this study)[117] were similar, however in the 2L+ group more patients had an ECOG status of 2-3 and median serum tryptase levels were higher.

Baseline characteristics of patients in EXPLORER are shown in Appendix M, Section M2.2. Overall, the AdvSM populations in EXPLORER and PATHFINDER are comparable, with similar age at baseline, ECOG performance status, and proportions of AdvSM subtype. Measures of mast cell disease burden (BM mast cell burden, serum tryptase level) were similar, although serum tryptase levels were higher in the PATHFINDER population. Fewer patients had received prior therapy in the PATHFINDER study, although a higher proportion had previously received midostaurin. This is not unexpected, considering the study timeframes and increasing use of midostaurin following its regulatory approval in the EU and US in 2017.

Table 8: Baseline characteristics of patients treated with 200 mg avapritinib starting dose in PATHFINDER

	Safety population			RAC-RE Population		
Characteristic	**2L+ (n=67)**	**1L (n=38)**	**All (n=105)**	**2L+ (n=51)**	**1L (n=30)**	**All (n=81)**
Age, median years (range)	68 (31, 86)	68 (39, 88)	68 (31, 88)	69 (31, 86)	68 (39, 88)	68 (31, 88)
Female, n (%)	26 (38.8)	18 (47.4)	44 (41.9)	15 (29.4)	14 (46.7)	29 (35.8)
ECOG performance status, n (%)						
0	16 (23.9)	6 (15.8)	22 (21.0)	12 (23.5)	5 (16.7)	17 (21.0)
1	31 (46.3)	25 (65.8)	56 (53.3)	23 (45.1)	19 (63.3)	42 (51.9)
2	14 (20.9)	5 (13.2)	19 (18.1)	11 (21.6)	4 (13.3)	15 (18.5)
3	6 (9.0)	2 (5.3)	8 (7.6)	5 (9.8)	2 (6.7)	7 (8.6)
AdvSM subtype, n (%)						
ASM	14	7	21	8	5	13
SM-AHN	41	28	69	31	22	53
MCL	12	3	15	12	3	15
***KIT* D816V, n (%)**	61 (91.0)	33 (86.8)	94 (89.5)	46 (90.2)	25 (83.3)	71 (87.7)
***KIT* D816V VAF, median % (range)**	19.6 (0.0, 47.5)	5.5 (0.0, 45.4)	15.0 (0.0, 47.5)	25.9 (0.0, 46.7)	7.8 (0.0, 45.3)	19.4 (0.0, 46.7)
S/A/R mutation, n (%)	24 (35.8)	23 (60.5)	47 (44.8)	19 (37.3)	20 (66.7)	39 (48.1)
BM mast cell burden, median % (range)	50.0	35.0	50.0	70.0	40.0	50.0

Characteristic	Safety population			RAC-RE Population		
	2L+ (n=67)	1L (n=38)	All (n=105)	2L+ (n=51)	1L (n=30)	All (n=81)
	(1.0, 95.0)	(3.0, 90.0)	(1.0, 95.0)	(1.0, 95.0)	(1.0, 90.0)	(1.0, 95.0)
Serum tryptase level, median ng/mL (range)	312.0 (23.8, 1600.0)	178.1 (37.3, 1336.0)	259.2 (23.8, 1600.0)	334.0 (23.8, 1600.0)	189.0 (37.3, 1336.0)	312.0 (23.8, 1600.0)
Spleen volume, median mL (range)	781.6 (44.2, 2652.2)	863.5 (149.8, 2897.1)	829.8 (44.2, 2897.1)	1030.7 (44.2, 2652.2)	901.8 (149.8, 2897.1)	944.1 (44.2, 2897.1)
Prior systemic therapy*, n (%)						
Midostaurin	56 (83.6)	–	56 (53.3)	41 (80.4)	–	41 (50.6)
Cladribine	10 (14.9)	–	10 (9.5)	8 (15.7)	–	8 (9.9)
Interferon alpha	10 (14.9)	–	10 (9.5)	7 (13.7)	–	7 (8.6)
Hydroxycarbamide	5 (7.5)	–	5 (4.8)	5 (9.8)	–	5 (6.2)
Imatinib	5 (7.5)	–	5 (4.8)	5 (9.8)	–	5 (6.2)
Dasatinib	4 (6.0)	–	4 (3.8)	4 (7.8)	–	4 (4.9)
Azacitidine	3 (4.5)	–	3 (2.9)	3 (5.9)	–	3 (3.7)
Investigational antineoplastic drugs	2 (3.0)	–	2 (1.9)	2 (3.9)	–	2 (2.5)
Peg-interferon alpha	2 (3.0)	–	2 (1.9)	1 (2.0)	–	1 (1.2)
Stem cells nos	2 (3.0)	–	2 (1.9)	1 (2.0)	–	1 (1.2)
Brentuximab vedotin	1 (1.5)	–	1 (1.0)	0	–	0
Decitabine	1 (1.5)	–	1 (1.0)	1 (2.0)	–	1 (1.2)
Nilotinib	1 (1.5)	–	1 (1.0)	1 (2.0)	–	1 (1.2)
Protein kinase inhibitors	1 (1.5)	–	1 (1.0)	1 (2.0)	–	1 (1.2)
Purine analogues	1 (1.5)	–	1 (1.0)	1 (2.0)	–	1 (1.2)
Radiotherapy	1 (1.5)	–	1 (1.0)	0	–	0
Thalidomide	1 (1.5)	–	1 (1.0)	1 (2.0)	–	1 (1.2)

Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e, patients who have received one or more prior systemic therapies; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; RAC-RE, response assessment committee response-evaluable; S/A/R, *SRSF2*/*ASXL1*/*RUNX1* gene panel; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; VAF, variant allele fraction. Note: The safety population includes all the patients in the RAC-RE population.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Details on baseline characteristics of the external control study (BLU-285-2405) and comparison with EXPLORER and PATHFINDER are provided in Section B2.9.

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 studies.

B.2.4.1 Statistical analysis and definition of study groups

An overview of the statistical methodology for PATHFINDER is shown in Table 9. An overview of the statistical methodology of EXPLORER is shown in Appendix M, Section M.2.3. Methodology for analysis of the external control study and an inverse probability of treatment-weighted analysis with the avapritinib studies is described in Section B.2.9.

Table 9. Summary of statistical analyses - PATHFINDER

Trial number (acronym)	**PATHFINDER (BLU-285-2202)**
Hypothesis objective	The primary objective was to determine study steering committee (SSC)- adjudicated ORR by mIWG-MRT-ECNM criteria: • The primary efficacy endpoint was adjudicated ORR (CR+CRh+PR+CI) based mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort 1 only)
Statistical analysis	Primary ORR analysis will be based on SSC adjudicated responses in the response-evaluable population. ORR will be estimated using frequency, percentage, and two-sided 95% confidence intervals based on the exact binomial distribution (Clopper-Pearson). Statistical test on binomial proportion against a null of 28% will be performed using one sided α=0.025. Wald test p-value will be presented.
Sample size, power calculation	The sample size of approximately 63 patients in Cohort 1 was estimated based on the primary objective and was intended to provide 93.5% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis ORR of 28% vs. the alternative ORR of 50%. Enrolment of the SM-AHN subgroup was capped at 70% of 63 patients (i.e. maximum of 45 patients) to ensure the study population reflects the general AdvSM patient population. This sample size also allowed statistical testing of the key secondary objective and was intended to provide >90% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis mean change of TSS ≥0 vs. the alternative mean change of TSS ≤−10. All treated patients in Cohort 1 and Cohort 2 were included in the analysis. Testing for this key secondary endpoint was sequential to ensure control of the study wise type I error rate (i.e., it was only performed when the null hypothesis for the primary objective was rejected).

	The non-mIWG-MRT-ECNM evaluable cohort (Cohort 2) of approximately 40 patients, for a total of 103, was intended for an approximate 88% probability of observing ≥1 AE at 2% frequency, instead of 3.5% frequency with 60 patients.
Analysis populations	• **Safety Population:** All patients who received ≥1 dose of avapritinib; • **RAC-RE Population:** All patients who received ≥1 dose of avapritinib, are deemed evaluable per mIWG-MRT-ECNM criteria at baseline as assessed by SSC review, and had one of the following conditions: o ≥2 complete postbaseline BM biopsy assessments, and had been on study for ≥6 cycles (6×28=168 days); o had an EOS Visit. • **PPRE:** All patients who received ≥1 dose of avapritinib, and had one of the following conditions: o ≥ 2 complete postbaseline BM biopsy assessments, and had been on study for ≥6 cycles (6×28=168 days); o had an EOS Visit. The RAC-RE population (equivalent to the BLU-285-2101 RAC-RE population) was used for the primary efficacy analysis, and all secondary efficacy analyses related to response, such as objective response, TTR, DOR, PFS, CI rate, and clinical benefit rate. The safety population was used for the key secondary analysis, PRO analyses, and efficacy analyses that were not based on mIWG-MRT-ECNM response criteria. The PPRE population was used as analysis population for pure pathologic response, such as objective response rate, TTR, DOR, PFS.
Subgroup analysis	Prespecified subgroups are listed in Table 7.
Interim analyses	There was one planned interim analysis when 32 patients (with the SM-AHN subgroup capped at approximately 70%) enrolled in the Cohort 1 were evaluable for response. If the 1-sided p-value was <0.00625, the null hypothesis was to be rejected, and avapritinib deemed effective in treating patients with AdvSM and the interim analysis to be used to support a marketing application. If the 1-sided p-value was ≥0.00625 at the interim analysis, the final analysis was to be used to support a marketing application. The final analysis of the primary efficacy endpoint will occur after all 63 patients (with the SM-AHN subgroup capped at approximately 70%) are enrolled in the Cohort 1 and have had the opportunity to receive avapritinib treatment for at least 10 cycles or have discontinued treatment earlier. The final primary efficacy analysis will be tested at 1-sided alpha level of 0.02178.

Data management, patient withdrawals	Details of data imputation are provided in the statistical analysis plan. Patients could withdraw or be withdrawn from study treatments at any time for any of the following reasons: disease progression; AE; death; lost to follow-up; protocol deviation; withdrawal of consent; pregnancy investigator decision; non-compliance; sponsor decision; other.

Abbreviations: AdvSM, advanced systemic mastocytosis; AE, adverse event; BM, bone marrow; CI, clinical improvement / confidence interval; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts MC, mast cell; DOR, duration of response; EOS, end of study; mIWG-MRT-ECNM criteria, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis. OD, once per day; ORR, overall response rate; PFS, progression-free survival; PPRE, Pure Pathologic Response-Evaluable; PR, partial remission; PRO, patient-reported outcome; RAC-RE, response evaluation committee response-evaluable; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; SSC, study steering committee; TSS, total symptom score, TTR, time to response

Source: MHRA Summary of clinical efficacy 2.7.3, Blueprint Medicines [data on file];[99] PATHFINDER CSR, Blueprint Medicines, 2020 [data on file];[102] PATHFINDER SAP, Blueprint Medicines, 2020 [data on file][103]

B.2.4.2 Patient disposition

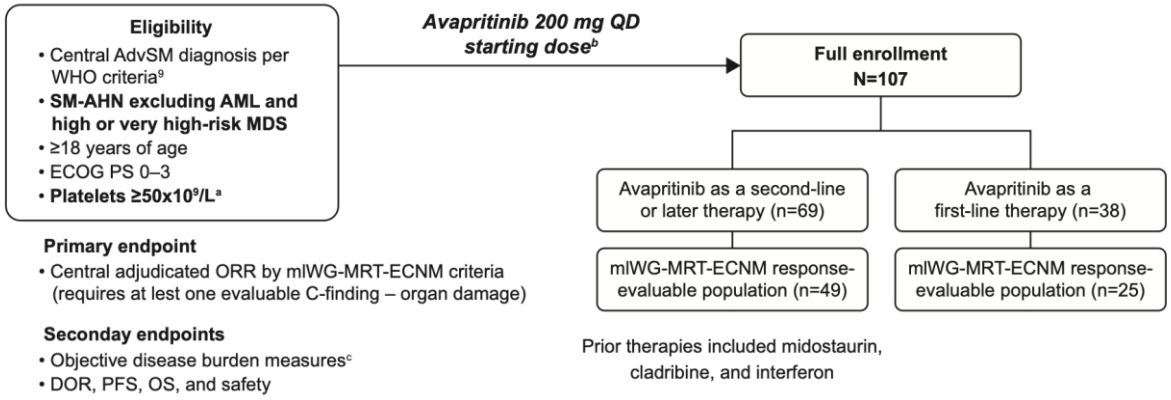
Patient disposition of PATHFINDER and the ECS are described in Sections B.2.4.2.1 and B.2.4.2.2. Patient disposition of EXPLORER is described in Appendix M, Section M2.4.

B.2.4.2.1 PATHFINDER

The PATHFINDER study is ongoing. A prespecified interim analysis of efficacy was triggered when 32 patients enrolled in Cohort 1 achieved sufficient follow-up.[48] An interim analysis of safety was also performed in 62 eligible patients from both cohorts (safety population).[48] Whilst the 2021 data cut-off was used to support regulatory applications in the EU and UK, updated data (September 2022 data-cut-off) are available (Table 6).

As of the September 2022 data cut-off, 107 patients have been enrolled (ASM, n=21; SM-AHN, n=71; MCL, n=15; Figure 9).[73] This includes patients who received avapritinib as a first-line therapy (1L; n=38, all started avapritinib at 200 mg daily) and patients who received avapritinib after one or more prior systemic therapies (2L+; n=69, 67 of whom started avapritinib at 200 mg daily). A total of 83 patients were included in the RAC-RE cohort and can be assessed via the primary endpoint, response to therapy (1L: n=30, 2L+: n=53 (n=51 patients who initiated avapritinib at 200 mg.

Figure 9. Summary of patient enrolment and disposition – PATHFINDER



[a]Implemented in 2019 to reduce risk of intracranial bleeding. [b]Two patients initiated 100 mg OD avapritinib, all others initiated at 200 mg OD. [c]Disease burden measures include BM MCs, serum tryptase, KIT D816V VAF, and spleen volume. No type 1 error control for these endpoints.

Abbreviations: AdvSM, advanced systemic mastocytosis; AML, acute myeloid leukaemia; BM, bone marrow; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; MDS, myelodysplasia syndrome; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; OD, once daily; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily (also known as OD); SM-AHN, systemic mastocytosis with associated haematologic neoplasm; VAF, variant allele fraction; WHO, World Health Organization
Source: Gotlib et al., 2023[73]

A summary of patient disposition in PATHFINDER as of the September 2022 data cut-off, 200 mg avapritinib starting dose, is provided in Table 10. As of the cut-off, of the 105 patients treated with 200 mg of avapritinib in PATHFINDER, 47 have discontinued treatment and 34 have discontinued from the study. Primary reasons for study discontinuation included death (20 patients) and withdrawal of consent (9 patients), while primary reasons for treatment discontinuation included disease progression (6 patients), AEs (26 patients, including 12 that were assessed as treatment-related by the Investigators), withdrawal of consent (4 patients), and sponsor decision (5 patients).

Table 10. Patient disposition in patients treated with 200 mg avapritinib starting dose in PATHFINDER

	Safety population (n=105)			RAC-RE Population (n=81)		
	2L+ (n=67) n (%)	1L (n=38) n (%)	All (n=105) n (%)	2L+ (n=51) n (%)	1L (n=30) n (%)	All (n=81) n (%)
Discontinued from treatment	35 (52.2)	12 (31.6)	47 (44.8)	23 (45.1)	8 (26.7)	31 (38.3)
Continuing on treatment	32 (47.8)	26 (68.4)	58 (55.2)	28 (54.9)	22 (73.3)	50 (61.7)
Discontinued from study	25 (37.3)	9 (23.7)	34 (32.4)	19 (37.3)	6 (20.0)	25 (30.9)
Reasons for discontinuation of treatment						
Disease progression	[redacted]					
AE(s)	[redacted]					

	Safety population (n=105)			RAC-RE Population (n=81)		
	2L+ (n=67) n (%)	1L (n=38) n (%)	All (n=105) n (%)	2L+ (n=51) n (%)	1L (n=30) n (%)	All (n=81) n (%)
Related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative/other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for discontinuation of study						
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE(s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative/other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiation of another antineoplastic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e, patients who have received one or more prior systemic therapies; AE, adverse event; AML, acute myeloid leukaemia; RAC-RE; Response Assessment Committee response-evaluable. Note: The safety population includes all patients in the RAC-RE population.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.4.2.2 External control study

Data were collected from 161 real-world patients who were treated at study sites between 1 January, 2009, and 4 October, 2021. Of these, 20 (12.4%) had missing data on a key covariate (specifically, performance status) that was deemed critical for inverse probability of treatment weights (IPTW), and thus were excluded from the analytical sample. Therefore, the analytical sample consisted of 141 real-world patients in the BAT cohort, who were compared with 176 patients in the avapritinib cohort enrolled in the EXPLORER (N=69) and PATHFINDER (N=107) trials. The avapritinib cohort consisted of patients with confirmed AdvSM diagnosis of known disease subtype, and who initiated treatment with any dose of avapritinib. Patients in the avapritinib cohort were followed from March 2016 to the time of the specified data cut-off (either the EXPLORER/PATHFINDER April 2021 data cut-offs or the PATHFINDER September 2022 data cut-off).

The collection of retrospective data from the real-world cohort is completed with no further data cut-offs post October 2021.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Quality assessment

See Appendix D for the quality assessment of the included studies.

B.2.5.2 Limitations of the evidence base

The clinical studies investigating avapritinib are single-arm studies and there are no head-to head studies comparing avapritinib against the comparators in the scope. To generate real-world data on therapies used to treat patients with AdvSM Blueprint Medicines has carried out an external control study. Strengths and limitations of the clinical trial data and comparative analyses are further discussed in Sections B.2.9.4 and B2.12.

B.2.6 Clinical effectiveness results of the relevant studies

The Phase 2 PATHFINDER study is the main clinical study supporting this submission and, as such, results from this study are presented throughout the clinical effectiveness section. To further support the clinical efficacy of avapritinib, longer-term results from the Phase 1 EXPLORER study are provided in Appendix M, Section M3. As previously noted, in the EXPLORER study only 20 of 69 patients with AdvSM received the expected UK licensed starting dose of 200 mg OD. These results are therefore supportive only.

B.2.6.1 PATHFINDER

In an interim analysis of the Phase 2 PATHFINDER study (data cut-off: June 2020) avapritinib demonstrated rapid and durable responses in patients with AdvSM. Avapritinib led to reductions in disease burden, improved patient symptoms and HRQoL, and elicited molecular responses of KIT D816V. Data from the interim analysis are provided in Appendix M, Section M4.

As of the April 2021 data cut-off (provided to support the MHRA application), avapritinib continued to demonstrate high levels of efficacy (for further details see Appendix M, Section 42).[99]

Data from the latest available data cut-off (September 2022) in patients who received a starting dose of 200 mg avapritinib in the PATHFINDER study (n=105) are included in the economic model and are provided below. Data from patients treated with all starting doses of avapritinib in PATHFINDER (n=107; including two patients that received a starting dose of 100 mg), as of the September 2022 data cut-off, have also been reported and are provided in Appendix M, Section M4.

B.2.6.1.1 Response to treatment according to mIWG-MRT-ECNM criteria

As of the September 2022 cut-off, avapritinib continued to demonstrate high levels of efficacy in patients with AdvSM who initiated avapritinib at a dose of 200 mg (Table 11). Specifically, an ORR of 74.1% (95% confidence interval [CI]: 63.1%, 83.2%) was observed, including a CR rate of 13.6% and CRh rate of 13.6%

In patients not receiving any prior systemic therapy, ORR was 90.0% (95% CI: 73.5, 97.9) compared to 64.7% (95% CI: 50.1, 77.6) in patients who had received prior systemic therapy.

Rapid and durable responses to avapritinib were observed. Median time to response was 2.2 months (range: 0.3 to 15 months) and median time to CR or CRh was 9.1 months (range 1.8 to 26 months). As of the data cut-off, median DOR for all responders was not reached. Of patients who demonstrated a response (ORR) to avapritinib, 86.7% maintained this response as of the data cut-off.

Table 11. Response to therapy (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose)

	AdvSM subtype			Treatment history		All AdvSM (n=81)
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	
ORR*, n (%) [95% confidence interval]	10 (76.9) [46.2, 95.0]	40 (75.5) [61.7, 86.2]	10 (66.7) [38.4, 88.2]	33 (64.7) [50.1, 77.6]	27 (90.0) [73.5, 97.9]	60 (74.1) [63.1, 83.2]
Best response, n (%)						
CR	0	8 (15.1)	3 (20.0)	5 (9.8)	6 (20.0)	11 (13.6)
CRh	2 (15.4)	9 (17.0)	0	5 (9.8)	6 (20.0)	11 (13.6)
PR	8 (61.5)	20 (37.7)	7 (46.7)	20 (39.2)	15 (50.0)	35 (43.2)
CI	0	3 (5.7)	0	3 (5.9)	0	3 (3.7)
Duration of response						
Median DOR, months (95% confidence interval)	NE (26.5, NE)	NE (37.1, NE)	NE (NE, NE)	NE	37.1 (37.1, NE)	NE (37.1, NE)
Censored, n (%)	8 (80.0)	34 (85.0)	10 (100)	28 (84.8)	24 (88.9)	52 (86.7)
DOR rate at 12 months, KM estimate, % (95% confidence interval)	88.9 (68.4, 100.0)	94.6 (87.3, 100.0)	100.0 (100.0, 100.0)	93.4 (84.6, 100.0)	96.0 (88.3, 100.0)	94.6 (88.6, 100.0)
DOR rate at 24 months, KM estimate, % (95% confidence interval)	88.9 (68.4, 100.0)	86.3 (75.2, 97.5)	100.0 (100.0, 100.0)	86.6 (74.4, 98.8)	91.6 (80.5, 100.0)	88.8 (80.4, 97.3)
DOR rate at 36 months, KM estimate, % (95% confidence interval)	59.3 (9.9, 100.0)	86.3 (75.2, 97.5)	NR	81.2 (65.8, 96.6)	91.6 (80.5, 100.0)	84.6 (73.2, 96.0)
DOR rate at 42 months†, KM estimate, % (95% confidence interval)	NR	69.0 (37.5, 100.0)	NR	81.2 (65.8. 96.6)	NR	70.5 (43.5, 97.4)
Time to response						
Time to response (ORR), months, median (range)	2.1 (0.3, 15.0)	2.0 (0.5, 12.2)	7.3 (1.7, 12.2)	2.0 (0.5, 14.6)	2.0 (0.3, 15.0)	2.2 (0.3, 15.0)
Time to CR or CRh, months, median (range)	2.8 (1.8, 3.7)	9.0 (1.8, 25.8)	20.3 (9.3, 26.0)	12.1 (1.8, 26.0)	7.1 (1.9, 25.8)	9.1 (1.8, 26.0)

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, clinical improvement; CRh, complete remission with partial recovery of peripheral blood counts; DOR, duration of response; KM, Kaplan-Meier; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL, mast cell leukaemia; NR, not reported; NE, not evaluable; ORR, overall response rate; PR, partial remission; RAC-RE, response assessment committee response-evaluable; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm. *ORR is the sum of CR, CRh, PR, and CI. †This is the last available follow-up (data cut-off 9 September 2022). These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.6.1.2 Progression-free survival (secondary endpoint)

PFS in PATHFINDER patients (RAC-RE population) who initiated avapritinib at a dose of 200 mg is summarised in Table 12. As of the data cut-off, 61 (75.3%) patients were censored for analysis and 20 (24.7%) had had died or progressed in disease; median PFS has not been met.

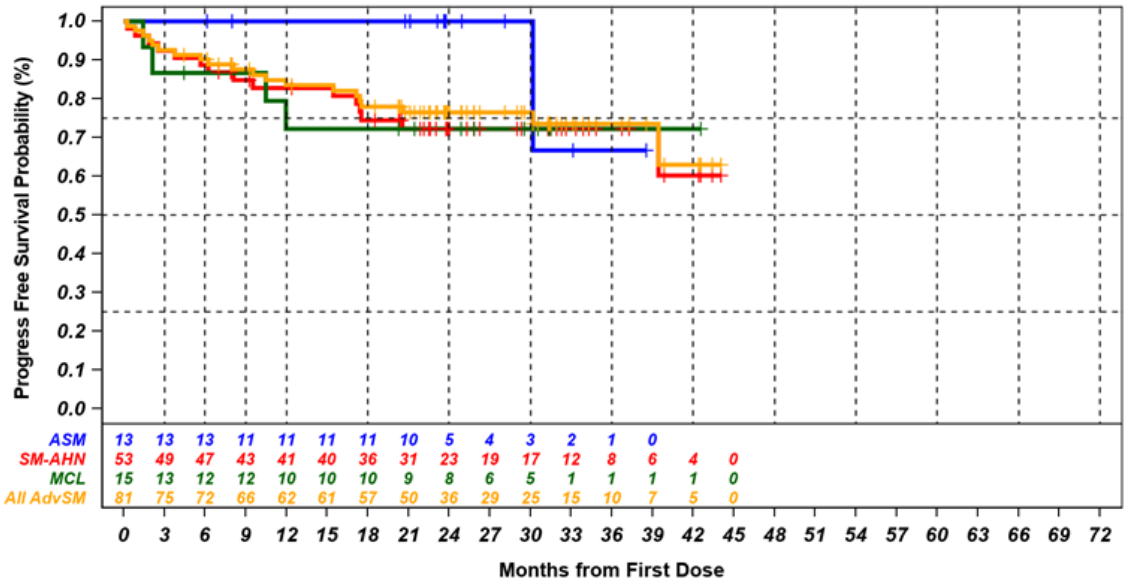
PFS Kaplan-Meier (KM) curves are presented for individual disease subtypes in Figure 10, and by prior systemic therapy in Figure 11. As of the data cut-off, median PFS of 39.4 months (95% CI: 39.4, not evaluable [NE]) was observed in patients who had not received prior systemic therapy median, and PFS has not been met in patients who had received prior systemic therapy.

Table 12. Progression-free survival (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose)

	AdvSM subtype			Treatment history		All AdvSM (n=81)
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	
Progression-free survival						
Events, n (%)	1 (7.7)	15 (28.3)	4 (26.7)	16 (31.4)	4 (13.3)	20 (24.7)
Censors, n (%)	12 (92.3)	38 (71.7)	11 (73.3)	35 (68.6)	26 (86.7)	61 (75.3)
Kaplan-Meier estimates						
Median PFS, months (95% CI)	NE (30.2, NE)	NE (39.4, NE)	NE (12.0, NE)	NE (30.2, NE)	39.4 (39.4, NE)	NE (39.4, NE)
12 months (95% CI)	100.0 (100.0, 100.0)	82.8 (72.6, 93.0)	72.2 (49.0, 95.4)	77.9 (66.3, 89.5)	93.0 (83.6, 100.0)	83.5 (75.2, 91.7)
24 months (95% CI)	100.0 (100.0, 100.0)	72.2 (59.7, 84.7)	72.2 (49.0, 95.4)	68.8 (55.5, 82.0)	89.4 (78.1, 100.0)	76.5 (66.9, 86.0)
36 months (95% CI)	66.7 (13.3, 100.0)	72.2 (59.7, 84.7)	72.2 (49.0, 95.4)	64.2 (49.1, 79.3)	89.4 (78.1, 100.0)	73.4 (62.5, 84.3)
42 months (95% CI)*	NR	60.2 (36.3, 84.1)	72.2 (49.0, 95.4)	64.2 (49.1, 79.3)	44.7 (0.0, 100.0)	62.9 (41.7, 84.2)

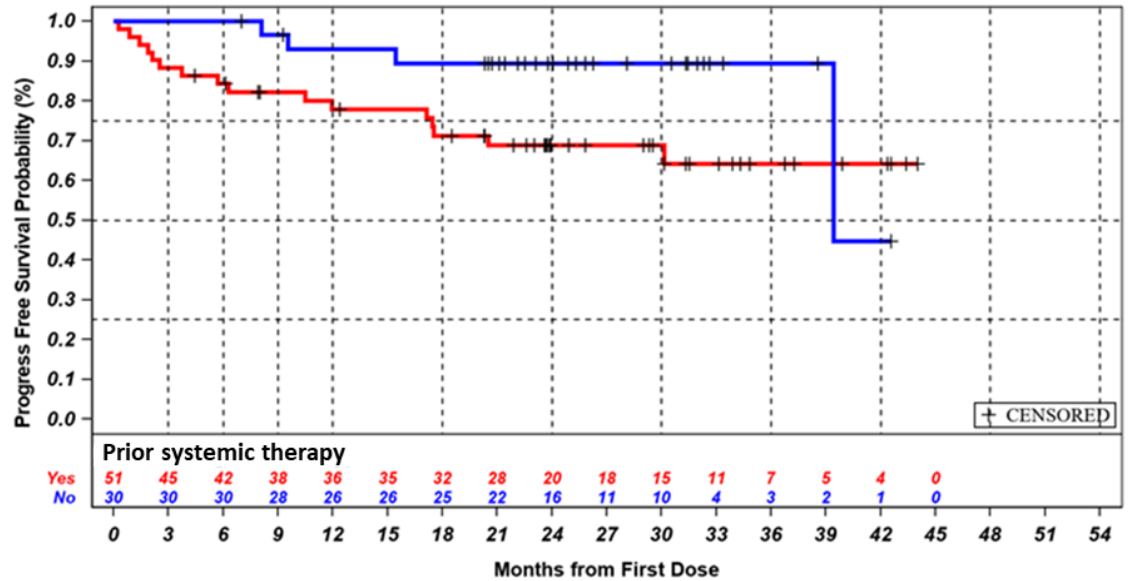
Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e, patients who have received one or more prior systemic therapies; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, confidence interval; KM, Kaplan-Meier; MCL, mast cell leukaemia; NR, not reported; NE, not evaluable; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with an associated haematological neoplasm. *This is the last available follow-up. Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Figure 10. Progression-free survival (PATHFINDER, RAC-RE, 200 mg avapritinib starting dose) by AdvSM subtype



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematological neoplasm. Note: Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Figure 11. Progression-free survival (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose) by prior systemic therapy



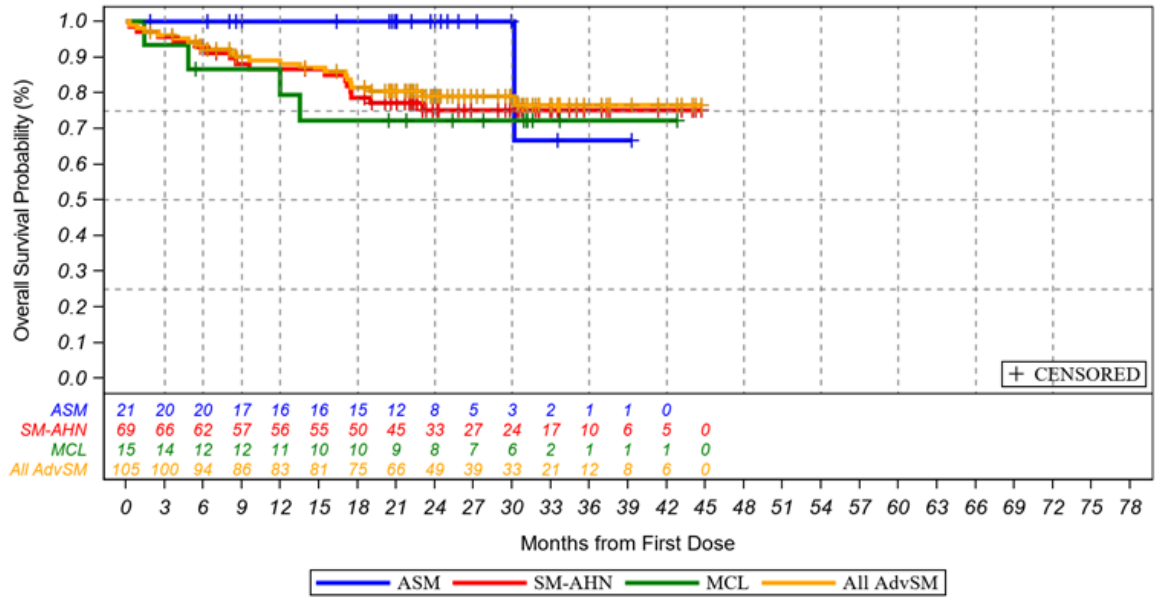
Abbreviations: RAC-RE, response assessment committee response-evaluable. Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.6.1.3 Overall survival (secondary endpoint)

Overall survival in PATHFINDER patients (safety population) who initiated avapritinib at a dose of 200 mg is presented in Figure 12. As of the data cut-off, median OS has not yet been reached in this population, 84 of 105 patients were alive, and the KM estimate for OS at 24 months was 79.0% (95% CI: 70.8%, 87.3%).

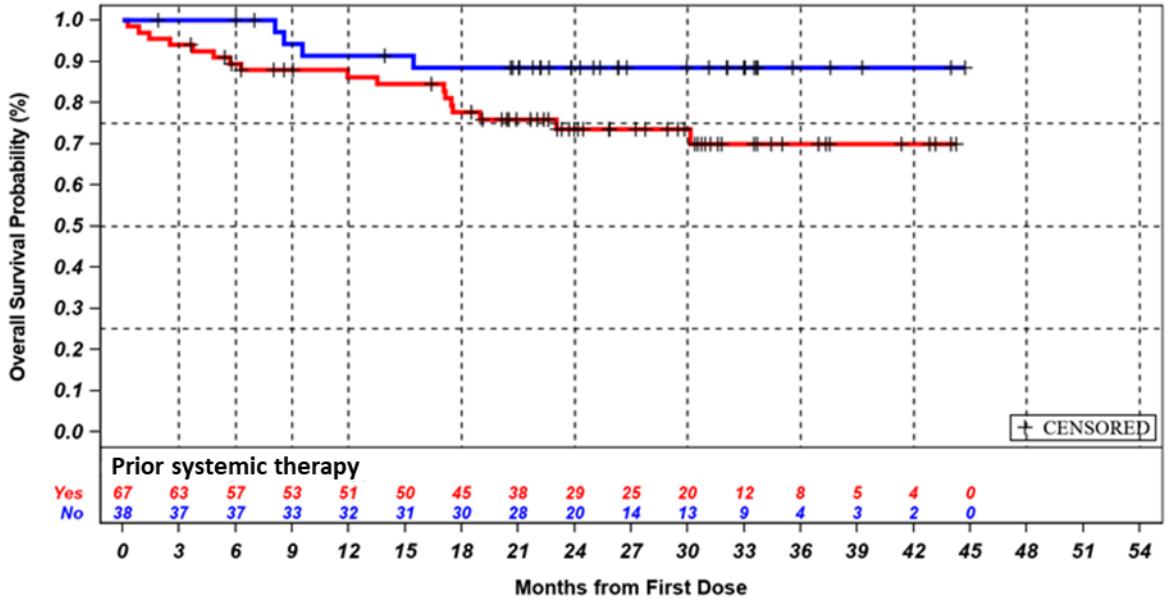
When considering prior systemic therapy use in PATHFINDER patients, median OS has not been met in either cohort (Figure 13). As of the data cut-off, in patients who had not received prior systemic therapy, 34 of 38 patients were alive, and the KM estimate for OS at 24 months was 88.5% (95% CI: 77.9%, 99.1%). In patients who had received prior systemic therapy 50 of 67 patients were alive, and the KM estimate for OS at 24 months was 73.6% (95% CI: 62.3%, 84.9%).

Figure 12. Overall survival (PATHFINDER, safety population, 200 mg avapritinib starting dose) by AdvSM subtype



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematological neoplasm. Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Figure 13. Overall survival (PATHFINDER, safety population, 200 mg avapritinib starting dose) by prior systemic therapy



Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.6.1.4 Objective measures of disease burden

Mast cells are the overabundant cell responsible for clinical manifestations of disease in AdvSM. Substantial reductions in measures of mast cell burden, including bone marrow mast cell percentage, serum tryptase levels, *KIT* D816V variant allele fraction (VAF), and spleen volume, were evident in patients in PATHFINDER who initiated avapritinib at a dose of 200 mg.

Reductions in bone marrow mast cells after initiating avapritinib were evident: 69.9% of patients had complete clearance of neoplastic bone marrow mast cell aggregates, and 87.4% of patients demonstrated a ≥50% reduction in bone marrow mast cells from baseline (Table 13).

In addition to reductions in mast cells, reductions in serum tryptase, which is understood to be a reliable biomarker in AdvSM,[118] were also observed. Serum tryptase levels were reduced to levels below 20 ng/mL in 61.9% of patients, which is notable considering that this threshold for serum tryptase level is one of four minor criteria used to establish a diagnosis of systemic mastocytosis. In addition, 91.4% of patients had a ≥50% reduction in serum tryptase level from baseline (Table 13).

It is critical to note that reductions in bone marrow mast cells and their mediators were driven by the targeted mechanism of action of avapritinib against the *KIT* D816V variant. Specifically, *KIT* D816 variant allele fraction (VAF) was reduced to less than 1% in 59.0% of patients and less

than 0.17% (below the limit of detection) in 35.2% of patients, and 82.9% of patients had a ≥50% reduction in *KIT* D816 VAF from baseline (Table 13).

Reductions in mast cells also led to decreased mast cell organ infiltration, which can reduce organomegaly and associated detrimental effects. Specifically, spleen volume was reduced by ≥35% in 69.9% of patients from baseline (Table 13).

Table 13. Changes in mast cell burden (PATHFINDER, safety population, 200 mg avapritinib starting dose)

	AdvSM subtype			Treatment history		All AdvSM
	ASM	SM-AHN	MCL	2L+	1L	
Bone marrow mast cells						
Patients with baseline evaluation, n	20	68	15	65	38	103
Total clearance, n (%)	16 (80.0)	50 (73.5)	6 (40.0)	43 (66.2)	29 (76.3)	72 (69.9)
≥50% reduction from baseline, n (%)	19 (95.0)	59 (86.8)	12 (80.0)	56 (86.2)	34 (89.5)	90 (87.4)
Serum tryptase						
Patients with baseline evaluation, n	21	69	15	67	38	105
Patients achieving <20 mg/mL, n (%)	15 (71.4)	45 (65.2)	5 (33.3)	38 (56.7)	27 (71.1)	65 (61.9)
≥50% reduction from baseline, n (%)	21 (100.0)	61 (88.4)	14 (93.3)	59 (88.1)	37 (97.4)	96 (91.4)
***KIT* D816V VAF**						
Patients with baseline evaluation, n	21	69	15	67	38	105
Patients with VAF <1%, n (%)	11 (52.4)	43 (62.3)	8 (53.3)	33 (49.3)	29 (76.3)	62 (59.0)
Patients with VAF <0.17%, n (%)	3 (14.3)	30 (43.5)	4 (26.7)	20 (29.9)	17 (44.7)	37 (35.2)
≥50% reduction from baseline, n (%)	18 (85.7)	59 (85.5)	10 (66.7)	51 (76.1)	36 (94.7)	87 (82.9)
Spleen volume						
Patients with baseline evaluation, n	21	67	15	65	38	103
≥35% reduction from baseline, n (%)	15 (71.4)	48 (71.6)	9 (60.0)	42 (64.6)	30 (78.9)	72 (69.9)

Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e., patients who have received one or more prior systemic therapies; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematological neoplasm; VAF, variant allele fraction.
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER. Data are based on the maximum recorded reduction from baseline.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

These data are supported by analysis of the EXPLORER study (see Appendix M, Section M3) as well as a pooled analysis of PATHFINDER and EXPLORER (referred to in Section B.2.8)

that demonstrated a normalisation of BM cellularity and histopathologic disease-related parameters, reduction in overall fibrosis and grade of fibrosis, and marked improvement in haematologic parameters. Patients treated with avapritinib were observed to have rapid (Week 8) and marked (Week 24) reductions in BM cellularity, neoplastic BM MC burden, characterised by a reduction of the total MC burden in BM biopsies, BM aspirates, and MC aggregates with a return to a normal morphologic appearance and immunophenotype and reduction in fibrosis. This was accompanied by a decrease in circulating MCs.[119]

B.2.6.1.5 Patient-reported outcomes

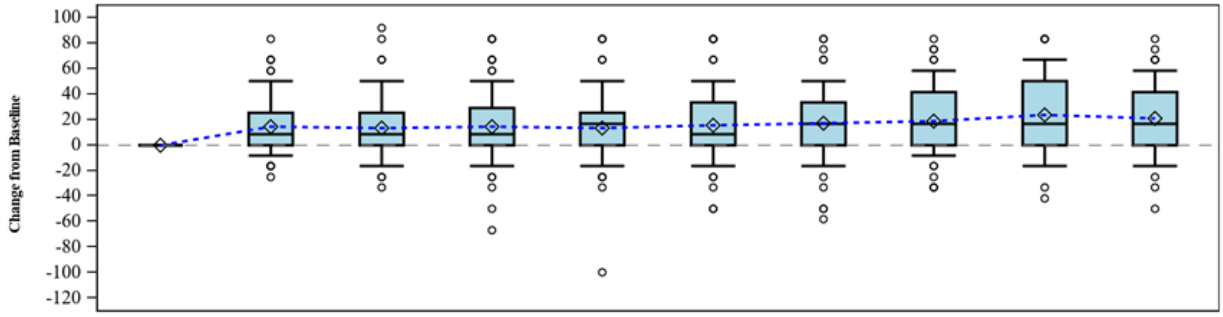
Patient-reported outcomes in patients in the PATHFINDER trial were assessed via AdvSM-SAF TSS, EORTC-QLC-C30 and PGIS assessments. At baseline, patients demonstrated the presence of symptoms associated with AdvSM, including fatigue and abdominal pain, which were the most severe symptoms.[48]

B.2.6.1.5.1 EORTC QLQ-C30

From baseline to cycle 17 of treatment (68 weeks; cycle length = 28 days), a mean increase in EORTC QLQ-C30 global health status score of 20.9 points (SD: 28.5) was observed, indicating improvement in overall HRQoL (Figure 14). This improvement from baseline is especially notable considering a minimal clinically important difference for EORTC QLQ-C30 of 5–10 points.[120] Patients treated with avapritinib on average had improvements in physical, emotional, social, and role-related function (Table 14).

When considering prior systemic therapy use in PATHFINDER patients, similar results were observed (Table 14). In patients who hadn't received prior systemic therapy, a mean increase in EORTC QLQ-C30 global health status score of 23.2 points (SD: 30.4) was observed from baseline to cycle 17 of treatment (68 weeks [cycle length = 28 days]). In patients who had received prior systemic therapy, a mean increase in EORTC QLQ-C30 global health status score of 19.5 points (SD: 27.7) was observed from baseline to cycle 17 of treatment (68 weeks [cycle length = 28 days]). Improvements in EORTC QLQ-C30 were also evident when considering just response-evaluable (RAC-RE) patients who started avapritinib at a dose of 200 mg (Table 15).

Figure 14. Change from baseline in EORTC QLQ-C30 global health status score (PATHFINDER, safety population, 200 mg avapritinib starting dose)



	Baseline	C1 D15	C2 D1	C3 D1	C5 D1	C7 D1	C9 D1	C11 D1	C14 D1	C17 D1
MIN	0	-25	-33.33	-66.67	-100	-50	-58.33	-33.33	-41.67	-50
Q1	0	0	0	0	0	0	0	0	0	0
MEDIAN	0	8.3333	8.3333	8.3333	16.667	8.3333	16.667	16.667	16.667	16.667
Q3	0	25	25	29.167	25	33.333	33.333	41.667	50	41.667
MAX	0	83.333	91.667	83.333	83.333	83.333	83.333	83.333	83.333	83.333
MEAN	0	14.357	13.333	14.479	13.48	15.404	17.077	18.683	23.397	20.915
STD	0	22.591	24.254	27.994	29.613	30.671	29.714	28.014	31.182	28.498
N	97	83	80	80	68	66	61	62	52	51

Abbreviations: CX, cycle X; DX, day X; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; Q1, first quartile; Q3, third quartile; STD, standard deviation. Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Table 14. Change from baseline in EORTC QLQ-C30 domains (PATHFINDER, safety population, 200 mg avapritinib starting dose)

	Mean change from baseline to Cycle 17		
EORTC QLQ-C30 domain	**All AdvSM**	**1L**	**2L+**
Physical functioning	13.5 points (SD: 25.3)	13.7 points (SD: 25.5)	13.3 points (SD: 25.5)
Role functioning	18.0 points (SD: 39.4)	14.9 points (SD: 47.1)	19.9 points (SD: 34.5)
Emotional functioning	11.3 points (SD: 26.1)	12.7 points (SD: 32.1)	10.4 points (SD: 22.4)
Cognitive functioning	–4.2 points (SD: 18.2)	–3.5 points (SD: 18.9)	–4.7 points (SD: 18.1)
Social functioning	18.0 points (SD: 37.8)	21.1 points (SD: 42.6)	16.1 points (SD: 35.3)
Global health status score	**20.9 points (SD: 28.5)**	**23.2 points (SD: 30.4)**	**19.5 points (SD: 27.7)**

Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e., patients who have received one or more prior systemic therapies; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; SD, standard deviation. Note: One cycle is equal to 28 days. Increases in score indicate improvement. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Table 15. Change from baseline in EORTC QLQ-C30 domains (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose)

	Mean change from baseline to Cycle 17		
EORTC QLQ-C30 domain	**All AdvSM**	**1L**	**2L+**
Physical functioning	19.5 points (SD: 25.2)	16.3 points (SD: 26.3)	21.8 points (SD: 24.7)
Role functioning	23.2 points (SD: 38.9)	18.8 points (SD: 44.3)	26.5 points (SD: 35.1)
Emotional functioning	14.5 points (SD: 27.4)	16.7 points (SD: 32.6)	13.0 points (SD: 23.7)
Cognitive functioning	–1.7 points (SD: 19.0)	–1.0 points (SD: 18.7)	–2.2 points (SD: 19.7)
Social functioning	28.2 points (SD: 35.5)	31.3 points (SD: 37.9)	26.1 points (SD: 34.4)
Global health status score	**25.9 points (SD: 29.9)**	**25.0 points (SD: 32.6)**	**26.5 points (SD: 28.5)**

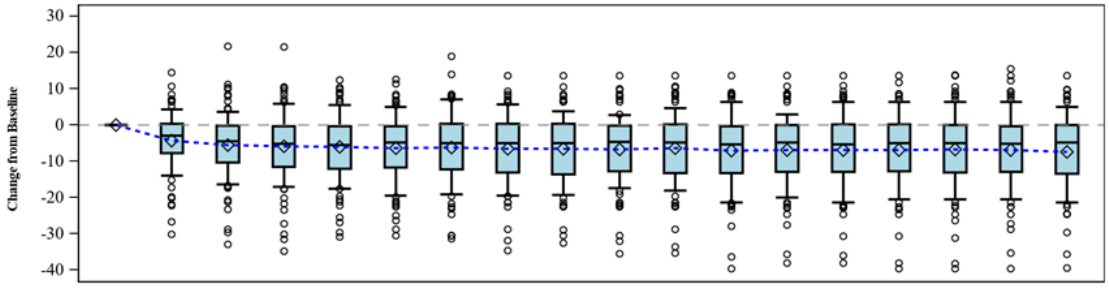
Abbreviations: 1L, first line of therapy, i.e., patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e., patients who have received one or more prior systemic therapies; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; SD, standard deviation. Note: One cycle is equal to 28 days. Increases in score indicate improvement. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.6.1.5.2 AdvSM Symptom Assessment Form

Improvement in HRQoL was also evident in patients treated with avapritinib at a starting dose of 200 mg via the AdvSM-SAF, as a decrease in mean TSS of 7.4 points (SD: 10.4) was demonstrated from baseline to cycle 18 (72 weeks) of treatment (Figure 15).

In patients who had not received prior systemic therapy, a decrease in mean TSS of 8.0 points (SD: 9.0) was demonstrated from baseline to cycle 18 (72 weeks; Figure 16). In patients who had received prior systemic therapy, a decrease in mean TSS of 7.1 points (SD: 11.1) was demonstrated from baseline to cycle 18 (72 weeks; Figure 17).

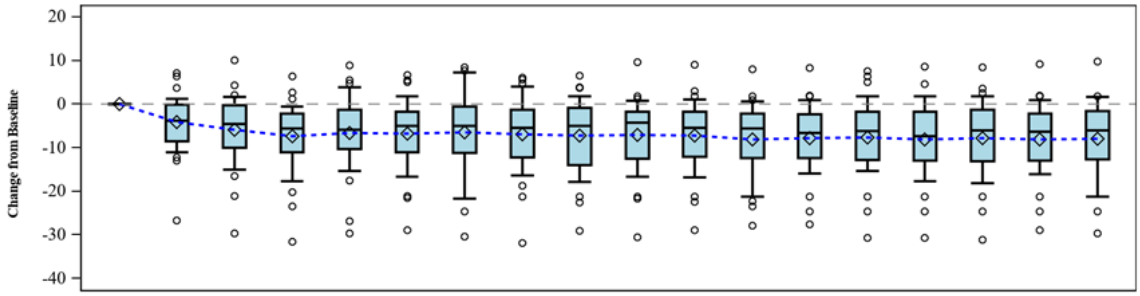
Figure 15. Change from baseline in AdvSM-SAF TSS (PATHFINDER, safety population, 200 mg avapritinib starting dose)



	Baseline	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1
MIN	0	-30.14	-32.86	-34.88	-30.9	-30.57	-31.43	-34.57	-32.57	-35.43	-35.38	-39.71	-38.14	-38	-39.57	-39.71	-39.57	-39.4
Q1	0	-7.821	-10.29	-11.46	-12.14	-11.71	-12.29	-13.07	-13.57	-12.76	-13.29	-13.29	-13	-13	-12.71	-13.14	-12.98	-13.43
MEDIAN	0	-2.929	-4.5	-5.143	-5.429	-4.857	-5	-4.917	-4.952	-4.714	-4.857	-5.286	-4.786	-5.286	-5	-5	-5.143	-4.857
Q3	0	0.4286	-0.143	-0.286	-0.286	-0.286	0.2857	0.3452	0.3333	-0.143	0.1429	-0.286	-0.071	0.1667	0.1667	0	-0.286	0
MAX	0	14.429	21.714	21.571	12.429	12.571	18.905	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.714	15.571	13.571
MEAN	0	-4.22	-5.426	-5.861	-6.041	-6.359	-6.173	-6.537	-6.574	-6.644	-6.405	-7.073	-6.823	-6.919	-6.938	-6.768	-6.923	-7.353
STD	0	7.8511	9.1483	9.6846	9.2663	9.2211	9.9537	9.567	9.5799	9.3463	9.737	9.9175	9.8691	10.225	10.271	10.467	10.373	10.429
N	91	88	90	90	90	90	85	88	87	91	91	89	88	89	89	87	89	79
P-VALUE			<.0001				<.0001				<.0001							

Abbreviations: AdvSM-SAF, Advanced Systemic Mastocytosis Symptom Assessment Form; CX, cycle X; DX, day X; Q1, first quartile; Q3, third quartile; STD, standard deviation; TSS, total symptom score. Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER. Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

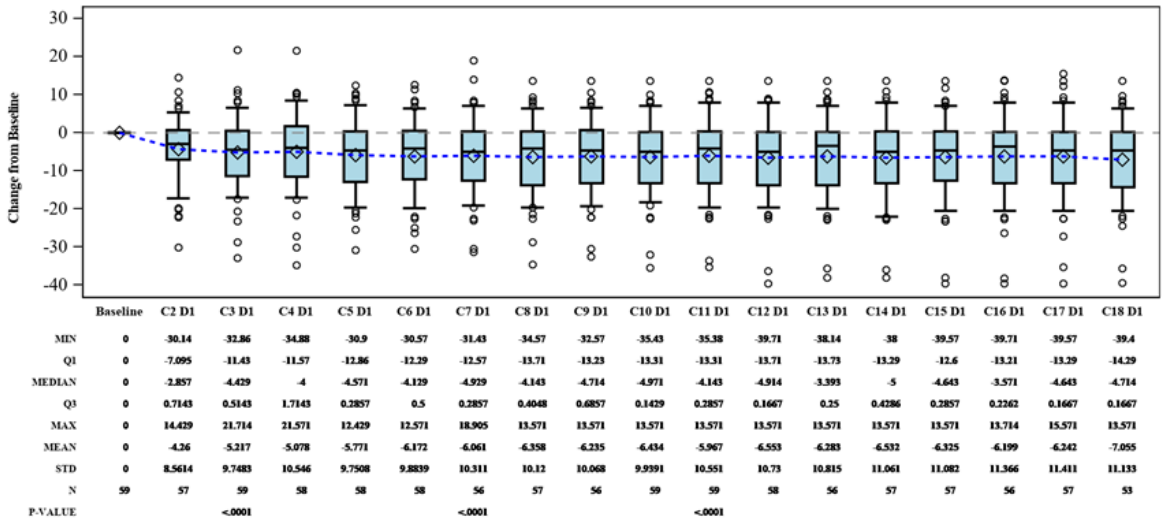
Figure 16. Change from baseline in AdvSM-SAF TSS (PATHFINDER, safety population, 1L, 200 mg avapritinib starting dose)



	Baseline	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1
MIN	0	-26.71	-29.71	-31.57	-29.57	-28.86	-30.43	-31.86	-29	-30.51	-28.86	-27.86	-27.57	-30.71	-30.71	-31.14	-28.86	-29.71
Q1	0	-8.548	-10	-10.99	-10.29	-11.05	-11.14	-12.14	-14	-12.51	-12.01	-12.43	-12.36	-12.86	-13	-13.14	-12.98	-12.71
MEDIAN	0	-3.857	-4.571	-5.571	-5.786	-5	-5	-5.429	-4.952	-4.286	-5.357	-5.571	-6.571	-6.214	-7.286	-6	-6.286	-6.071
Q3	0	-0.143	-0.286	-2.136	-1.286	-1.714	-0.571	-1.238	-0.833	-1.743	-1.743	-2.2	-2.357	-1.743	-1.743	-1.286	-2.171	-1.571
MAX	0	7.0714	10.048	6.3333	8.881	6.7143	8.4762	6.1429	6.5714	9.7143	9	8	8.2857	7.5714	8.5714	8.4286	9.1429	9.8571
MEAN	0	-4.146	-5.824	-7.279	-6.531	-6.7	-6.389	-6.867	-7.187	-7.031	-7.212	-8.046	-7.769	-7.607	-8.031	-7.795	-8.136	-7.961
STD	0	6.4749	8.0196	7.8451	8.4444	8.0189	9.3974	8.6083	8.7552	8.2791	8.1198	8.2623	8.0239	8.6603	8.7007	8.6911	8.236	8.9978
N	32	31	31	32	32	32	29	31	31	32	32	31	32	32	32	31	32	26
P-VALUE			0.0002				0.0005				<.0001							

Abbreviations: AdvSM-SAF, Advanced Systemic Mastocytosis Symptom Assessment Form; CX, cycle X; DX, day X; Q1, first quartile; Q3, third quartile; STD, standard deviation; TSS, total symptom score. Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and had not received prior systemic therapy. Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

Figure 17. Change from baseline in AdvSM-SAF TSS (PATHFINDER, safety population, 2L+, 200 mg avapritinib starting dose)



	Baseline	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1
MIN	0	-30.14	-32.86	-34.88	-30.9	-30.57	-31.43	-34.57	-32.57	-35.43	-35.38	-39.71	-38.14	-38	-39.57	-39.71	-39.57	-39.4
Q1	0	-7.095	-11.43	-11.57	-12.86	-12.29	-12.57	-13.71	-13.23	-13.31	-13.31	-13.71	-13.73	-13.29	-12.6	-13.21	-13.29	-14.29
MEDIAN	0	-2.857	-4.429	-4	-4.571	-4.129	-4.929	-4.143	-4.714	-4.971	-4.143	-4.914	-3.393	-5	-4.643	-3.571	-4.643	-4.714
Q3	0	0.7143	0.5143	1.7143	0.2857	0.5	0.2857	0.4048	0.6857	0.1429	0.2857	0.1667	0.25	0.4286	0.2857	0.2262	0.1667	0.1667
MAX	0	14.429	21.714	21.571	12.429	12.571	18.905	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.714	15.571	13.571
MEAN	0	-4.26	-5.217	-5.078	-5.771	-6.172	-6.061	-6.358	-6.235	-6.434	-5.967	-6.553	-6.283	-6.532	-6.325	-6.199	-6.242	-7.055
STD	0	8.5614	9.7483	10.546	9.7508	9.8839	10.311	10.12	10.068	9.9391	10.551	10.73	10.815	11.061	11.082	11.366	11.411	11.133
N	59	57	59	58	58	58	56	57	56	59	59	58	56	57	57	56	57	53
P-VALUE			<.0001				<.0001				<.0001							

Abbreviations: AdvSM-SAF, Advanced Systemic Mastocytosis Symptom Assessment Form; CX, cycle X; DX, day X; Q1, first quartile; Q3, third quartile; STD, standard deviation; TSS, total symptom score. Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and had received prior systemic therapy.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

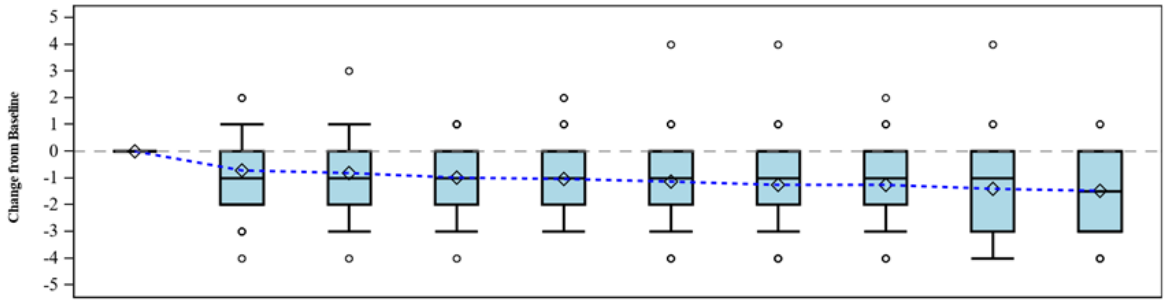
B.2.6.1.5.3 Patient Global Impression of Symptom Severity

The PGIS is a single item scale that assesses a patient's perception of disease symptoms at a point in time. The PGIS has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial.[48] The PGIS scale is scored from 0 (no symptoms), through 1 (minimal, symptoms that are easy to ignore); 2 (moderate, symptoms that are difficult to ignore); 3 (severe, symptoms that are very difficult to ignore) and 4 (very severe, symptoms that cannot be ignored).

Patient perception of their symptom severity further suggests improvements in HRQoL in patients treated with 200 mg of avapritinib. Specifically, a mean decrease in PGIS score of 1.5 points (SD: 1.4) was observed from baseline to cycle 17 (68 weeks) of treatment (Figure 18), meaning improvements in HRQoL.

Similar reductions were reported in patients who had received prior systemic therapy (mean decrease in PGIS score of 1.7 points [SD: 1.3]) and those who had not received prior systemic therapy (mean decrease in PGIS score of 1.2 points [SD: 1.5]).

Figure 18. Change from baseline in PGIS score (PATHFINDER, safety population, 200 mg avapritinib starting dose)



	Baseline	C1 D15	C2 D1	C3 D1	C5 D1	C7 D1	C9 D1	C11 D1	C14 D1	C17 D1
MIN	0	-4	-4	-4	-3	-4	-4	-4	-4	-4
Q1	0	-2	-2	-2	-2	-2	-2	-2	-3	-3
MEDIAN	0	-1	-1	-1	-1	-1	-1	-1	-1	-1.5
Q3	0	0	0	0	0	0	0	0	0	0
MAX	0	2	3	1	2	4	4	2	4	1
MEAN	0	-0.711	-0.823	-0.975	-1.044	-1.121	-1.262	-1.258	-1.392	-1.48
STD	0	1.205	1.2275	1.2115	1.3207	1.473	1.5045	1.3782	1.6258	1.3886
N	97	83	79	80	68	66	61	62	51	50

Abbreviations: CX, cycle X; DX, day X; Q1, first quartile; Q3, third quartile; PGIS, Patient Global Impression of Symptom Severity; STD, standard deviation. Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.6.2 EXPLORER

As previously noted, only a small number of patients (20 out of 69) in EXPLORER received the starting dose of 200 mg OD. Patients in the dose escalation group received avapritinib at a starting dose of 30 mg (n=3), 60 mg (n=4), 100 mg (n=1), 130 mg (n=1), 200 mg (n=3), 300 mg (n=4), or 400 mg (n=6) OD. In the dose-expansion group, patients received a starting dose of 200 mg (n=17) or 300 mg (n=30) OD.[76]

Maximum tolerated dose was not reached, and 200 mg and 300 mg daily were studied in dose-expansion cohorts.[75] In long-term analyses (as of April 5, 2022, with a median follow-up of 45 months):[76]

- ORR per mIWG-MRT-ECNM response criteria was 77% in all patients with AdvSM, 82% in treatment-naïve patients and 74% of patients treated with avapritinib as a 2L+ therapy.
- Among all patients treated with avapritinib, rapid (median time to PR or better, 2 months [range, 2–27]) and durable responses (median DOR not reached) were observed.
- Survival benefit across subtypes and regardless of prior therapy was ongoing with median OS not reached, and median PFS of 49 months (95% CI, 31–NE).
- Based on the safety, pharmacokinetics, and efficacy profile of avapritinib, a starting dose of 200 mg QD was recommended.

Further efficacy results of the EXPLORER study are described in Appendix M, Section M3.

B.2.6.3 UK Real-World Evidence

The clinical experience of AdvSM patients who have received avapritinib at 11 centres in the UK via an open-label CUP has been reported. Avapritinib was initiated in AdvSM patients with progressive disease-related symptoms and end-organ damage. The initial dose was adjusted according to tolerability and kept continuously until disease progression or unmanageable toxicity.[109]

B.2.6.3.1 Study cohort

In a cohort of 13 patients, with an age average of 68.8 years (range 57-76), 11 patients (84.6%) were diagnosed with SM-AHN; 81.8% with a concomitant diagnosis of CMML. Two patients (15.4%) were diagnosed with ASM. All patients harboured the D816V mutation, and eight patients (61.5%) presented with additional mutations; five with *SRSF2* and one with *ASXL1*. Baseline median blood parameters for this cohort were tryptase level of 168 ng/mL (range 91-811), alkaline phosphatase (ALP) of 437 IU/L (range 127-1235), albumin of 34.5 g/L (range 24-48) and a spleen size of 16.4 cm (range 12-26), measured radiologically.

On application of prognostic scores; IPSM 10 patients (76.9%) were classified as AdvSM-3/4 and Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis (MARS) seven patients (53.8%) were stratified as high risk.

B.2.6.3.2 Treatment

Ten patients (76.9%) received avapritinib as a first-line regime, and nine patients (69.2%) started at a dose of 200 mg OD. Three patients were previously treated with other regimes – one patient with midostaurin, one with cladribine and one with azacytidine.

B.2.6.3.3 Results

- Median duration of treatment was 503.7 days (range 75 - 1168 days).
- At response evaluation, nine patients (69.2%) had a tryptase level <20 ng/mL and 11 patients (84.6%) had normalised their ALP and albumin levels.
- None of the patients had a clinically enlarged spleen, with nine patients (69.2%) having a normal spleen size on abdominal ultrasound.

- The ORR (using the modified IWG-ECNM-MRT criteria) was 76.9% with a complete response (CR) or CR with partial haematologic recovery in 53.8% of patients. Eight patients had a complete pathological remission.
- At the last follow-up, three patients (23.1%) died; one from SM progression, one from haematemesis and one due to progression of the AHN component but had a partial response of the SM with avapritinib.
- Two patients with SM-AHN were referred for allo-HSCT as a curative treatment as a result of achieving a CR with avapritinib.

B.2.7 Subgroup analysis

PATHFINDER included prespecified subgroup analyses (Table 7). Analysis in subgroups by prior systemic therapy was a prespecified analysis and results are provided in Section B.2.6.1. Results in disease subtypes (ASM, SM-AHN, MCL) are also presented in Section B.2.6.1. This was not a pre-specified subgroup analysis; however, these subtypes are included in the scope and consideration of outcomes in the three disease subtypes is appropriate.

Prespecified subgroup analyses undertaken at the 23 June 2020 PATHFINDER data cut-off (pre-specified interim analysis) are provided in the CSR.[102] A detailed summary of the subgroup results of the pooled analyses presented during the UK regulatory application (April 2021 data cut-offs) is provided in the reference pack (MHRA 2.7.3 Summary of Clinical Efficacy).[99] There were no clinically meaningful differences in ORR across the subgroup categories (age, sex, region, prior midostaurin treatment, prior systemic therapy); the 95% confidence intervals around the ORR were wide and overlapping for each analysis.[99]

It should be noted that the pooled subgroup analyses included patients receiving all doses of avapritinib, and as such included patients who received a range of starting doses in the EXPLORER study, which may have an impact on the results. In addition, the inclusion of EXPLORER, in which a greater proportion of patients did not receive prior systemic therapy and which had a longer period of follow-up as of the data cut-off, may have impacted on the results. Taken alongside the small number of patients and heterogenous patient characteristics, the ability to draw any conclusions regarding subgroup comparison of outcomes in the pooled analysis is limited.

B.2.8 Meta-analysis

Since there are no RCTs for avapritinib, a pairwise meta-analysis was not possible. A pooled analysis of PATHFINDER and EXPLORER (April 2021 data cut-off for both studies) was

completed for the MHRA regulatory application, since at the data cut-off PATHFINDER data points were still limited.[99] The data presentation was focused on the expected UK licensed starting dose (200 mg OD) as well as patients treated with all starting doses. A summary of these results is provided in Appendix M, Sections M5 and M6. It should be noted that most of the patients in PATHFINDER study (105 out of 107) received the starting dose of avapritinib of 200 mg OD, whereas only a small number of patients (20 out of 69) from the EXPLORER study received the starting dose of 200 mg OD.

Further pooled analyses from the PATHFINDER and EXPLORER studies (April 2021 data cut-off for both studies) analyses demonstrated that avapritinib induced a high rate of clinically important responses in patients with previously untreated AdvSM, as well as in patients previously treated with at least one prior systemic treatment for AdvSM.[86,87] These analyses are not included in the economic analysis and are not described in further detail in this submission.

Similarly, pooled data from the EXPLORER and PATHFINDER April 2021 data cut-offs have been used in indirect comparisons (Section 2.9). However, due to sufficient data being available from the pivotal Phase 2 PATHFINDER study (September 2022 data cut-off), updated comparative analyses of the external control study include PATHFINDER alone and are used to inform the economic model.

Finally, a pooled analysis of EXPLORER (data cut-off May 27, 2020) and PATHFINDER (data cut-off June 23, 2020) demonstrated the effect of avapritinib on BM pathology including MC burden, morphology, and phenotype in BM, BM cellularity and fibrosis, as well as changes in selected haematologic parameters.[119] These data are reported in brief in Section B.2.6.1.4.

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 Overview of comparative evidence

The clinical evidence for avapritinib in people with AdvSM is from two single-arm studies: EXPLORER, a Phase 1 dose-finding trial, and PATHFINDER, a Phase 2 efficacy and safety trial.

- Comparative data against midostaurin and off-label therapies have been derived from two sources:
    - an inverse probability of treatment-weighted analysis using an ECS; BLU-285-2405), that collected real-world data on BAT, including midostaurin and cladribine,

- an MAIC in which individual patient data from the two avapritinib studies were indirectly compared with aggregate data from two Phase 2 studies evaluating midostaurin in people with AdvSM (D2201 and A2213).

- Both methods of comparative analysis have strengths and limitations, (see Section B.2.9.4), however the analyses from the ECS provide the most robust source of comparative evidence for the submission.
- Analyses from the ECS support the clinical and economic case and are described in Section B.2.9.2:
  - An analysis with pooled data from EXPLORER and PATHFINDER (April 2021 data cut-offs) provides comparative OS data against midostaurin and cladribine in any line of therapy.[53] Data are presented in the submission but do not inform the economic analysis since a later data cut was available for the key Phase 2 study, PATHFINDER.
  - An analysis with updated PATHFINDER data (September 2022 data cut-off) provides comparative data against midostaurin as a 1L treatment and cladribine as a 2L+ treatment, as well as against BAT, including midostaurin and cladribine, in patients who received at least one prior systemic therapy (2L+), and is included in the economic model (see Section B.3.4).
  - Several other analyses have been completed but are not presented in this submission (see Table 16 and Section B.2.9.2.2).
- The MAIC, that includes EXPLORER and PATHFINDER 2021 data cut-offs, provides comparative evidence for ORR, in addition to OS and CR, and informs a scenario analysis in the economic model exploring the impact of avapritinib on eligibility for allo-HSCT (Section B.2.9.3).[52]

Table 16. Indirect treatment comparison analyses

Avapritinib data	Comparison	Outcomes	Reference	Results presented
ECS				
EXPLORER and PATHFINDER (April 2021 data cut-offs)	• BAT: all lines • BAT: 1L • BAT: 2L+	• OS • DOT	Reiter et al. Leukemia 2022; 36: 2108–2120.[7]	Not presented
	• Midostaurin: all lines • Cladribine: all lines	• OS	Reiter et al. Hemasphere. 2022; 6(Suppl): 904-905.[53]	All-treatment-lines analysis (Pooled EXPLORER and PATHFINDER) Section B.2.9.2.4.1

PATHFINDER (September 2022 data cut-off) [outcomes/comparisons in bold are used to inform the economic model]	• **Midostaurin: 1L** • **Cladribine: 2L+** • BAT (excluding midostaurin): 1L • **BAT (including midostaurin): 2L+**	• **OS** • **DOT***	Blueprint Medicines, Data on file (2023)[106-108]	1L/2L+ analysis (Updated PATHFINDER), Sections B.2.9.2.4.2 and B.2.9.2.5.1.
MAIC				
EXPLORER and PATHFINDER (April 2021 data cut-offs)	• Midostaurin: all lines • Midostaurin: midostaurin-naïve • Midostaurin: 2L+	• OS • ORR • CR	Pilkington et al. Leukemia 2022; 36: 2108–2120[52]	Section B.2.9.3

*Scenario analysis
Abbreviations: 1L, first line of therapy; 2L+, second- or further-line of therapy; BAT, best available therapy; CR, complete remission; DOT, duration of treatment; ORR: overall response rate; OS, overall survival

B.2.9.2 External control study

The ECS (BLU-285-2405, described in Section B.2.3) aimed to generate real-world data on BAT used to treat patients with AdvSM, and to conduct comparative analyses of efficacy and safety outcomes between patients treated with avapritinib in EXPLORER and PATHFINDER vs. BAT in clinical practice.

This was a retrospective chart review study that collected longitudinal, individual-level data via medical chart abstraction on patients treated at centres of excellence in the UK, US, Austria, Spain, and Germany.

B.2.9.2.1 Indirect comparison methodology

Detailed methodology of the comparative analyses is provided in Appendix D. In brief:[7]

- Individual patient-level data for the BAT cohort were collected retrospectively, up to October 4, 2021, from the medical charts of adult patients with AdvSM, who received systemic treatment at participating study sites in Europe and the US on or after January 1, 2009.
- The avapritinib cohort consisted of either of patients treated with avapritinib in the EXPLORER and PATHFINDER trials, at any dose, included in the data cut-off as of April 2021, or the PATHFINDER trial included in the data cut-off as of September 2022.

- An integrated, unified dataset containing patient-level data from both cohorts was created, with harmonisation between the definition of outcomes and key baseline covariates.
- IPTW-weighted Cox proportional hazards models were used to assess the association between receiving avapritinib vs. BAT or individual therapies and outcomes of OS and DOT, adjusting for differences in key covariates defined a priori between the two treatment groups, while similarly weighted generalised estimating equation linear models were used for the analysis of change in serum tryptase from baseline.
- Key covariates included, but were not limited to, age, sex, Eastern Cooperative Oncology Group (ECOG) score, number of prior LOTs and types of prior therapy.
- Doubly robust estimation was used to adjust for covariates that remained unbalanced (standardised difference >10%) after IPTW-weighting, and robust variance estimation was used to account for the within-subject correlation of BAT cohort patients who contributed multiple LOTs as well as the application of weights.

B.2.9.2.2 Indirect treatment comparisons

Several analyses have been performed (Table 16).

Pooled results from EXPLORER and PATHFINDER (April 2021 data cut-off) have been compared to midostaurin and cladribine individually, across all lines of therapy.[53]

In order to provide longer-term data in the relevant population, the subgroup analyses comparing avapritinib with midostaurin and cladribine as 1L and 2L+ treatments, respectively, have been completed using the most recent available data cut-off from PATHFINDER (September 2022) and did not include data from EXPLORER.[106-108] Analyses comparing outcomes following avapritinib 2L+ to BAT 2L+ have also been completed. Out of the 89 lines of therapy included in the BAT 2L+ cohort with available agent-level information, common therapies included midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%).[121] These analyses inform the economic modelling and are presented below.

Subgroup analyses among 1L avapritinib patients vs.1L cladribine patients were not performed due to inadequate sample size of patients receiving 1L cladribine. In addition, subgroup analyses among 2L+ avapritinib patients vs. 2L+ midostaurin patients were not conducted due to the lack of comparability between the two cohorts (half of the 2L+ avapritinib patients had previously been treated with midostaurin).

Further analyses, published by Reiter et al (2022),[7] compared avapritinib (EXPLORER and PATHFINDER, April 2021 data cut-off) to BAT. Analyses were carried out for all treatment lines and in subgroups that received 1L treatment or 2L+ treatment. These analyses are not used in the economic model and are not presented here.

From the data available for BAT cohort, it was not possible to establish uniform evaluation of response to therapy. Unlike clinical trial settings, the assessment of response and disease progression in real-world clinical practice settings is not made consistently across patients and across physicians. In addition, patients may be followed less frequently compared to those of a similar level of disease in clinical trials, resulting in an overestimation of DOR in real-world studies.

Importantly, the indirect comparison could not provide comparative data on PFS, because it was not recorded in the retrospective real-world cohort. Even where time to progressive disease could be accurately determined, the progression criteria used in different centres were not generally consistent and were not consistent with those used in PATHFINDER. Assessment of progressive disease and PFS in PATHFINDER was made using mIWG-MRT-ECNM criteria (see Appendix M, Section M1). These criteria were not used in the real-world cohort, and as such were not collected for patients and could not been applied retrospectively in the retrospective ECS cohort receiving BAT.

An exploratory endpoint of real-world progression-free survival (rwPFS) was included in the ECS, where progressive disease was defined per PPR criteria, but the number of progressive events defined per PPR was extremely small in the BAT cohort. Therefore, outcomes assessed for real-world patients receiving BAT (including patients treated with midostaurin only and patients treated with cladribine only) were limited to the outcomes which could be most closely matched to those assessed for patients in the PATHFINDER trial.

B.2.9.2.3 Baseline characteristics

B.2.9.2.3.1 Pooled EXPLORER and PATHFINDER (all-treatment-lines analysis)

The pooled analysis included 176 patients treated with avapritinib in the pooled EXPLORER and PATHFINDER population (107 patients in the updated PATHFINDER population), 94 treated with midostaurin (contributing 99 lines of therapy) and 44 treated with cladribine (contributing 49 lines of therapy). The mean ages of the cohorts were similar, as were the proportions of female patients (Table 17).[53]

Prior to IPTW-weighting:[53]

- Fewer patients in the cladribine cohort (51.0%) had an SM-AHN subtype, compared to patients in the avapritinib (67.6%) or midostaurin (65.7%) cohorts, while more patients in the cladribine cohort had an ASM subtype.
- A greater proportion of patients in the midostaurin and cladribine cohorts (56.6% and 57.1%, respectively) had thrombocytopenia at baseline, compared to patients in the avapritinib cohort (38.1%).

- Patients in the avapritinib cohort were more likely to come from North America compared to patients in the midostaurin and cladribine cohorts, however, standards of care in North America are expected to be reflective of those in Europe and the UK and therefore this is not expected to introduce undue bias.

After weighting by stabilised, truncated IPTW weights, the standardised differences between avapritinib and the comparators decreased to <10% for most covariates, indicating the cohorts were comparable with regard to key covariates.

A total of 41.4% of the midostaurin cohort and 59.2% of the cladribine cohort had prior lines of systemic therapy, compared with 62.5% of the avapritinib cohort (Table 18). In the avapritinib and cladribine cohorts, patients were most frequently pre-treated with TKIs (52.3% and 42.9%, respectively), and the agent most commonly used was midostaurin. Patients in the midostaurin cohort were most frequently pre-treated with cytoreductive therapies (30.3%), and the agent most commonly used was cladribine.[53]

Table 17. Summary of baseline characteristics (pooled EXPLORER and PATHFINDER, April 2021 data cut-offs)

Baseline characteristics, unweighted sample[a]	Avapritinib cohort	Midostaurin cohort	p-value (avapritinib vs. midostaurin)[2]	Cladribine cohort	p-value (avapritinib vs. cladribine)[2]
Number of unique patients	N=176	N=94		N=44	
Number of lines of therapy	N=176	N=99		N=49	
Demographic characteristics					
Age (years)			0.359		0.250
Mean (SD)	66.3 (10.7)	67.1 (11.6)	-	64.6 (10.1)	-
Median (min, max)	68.0 (31.0, 88.0)	69.1 (25.8, 87.3)	-	66.1 (45.1, 87.5)	-
Sex, n (%)					
Female	73 (41.5%)	32 (32.3%)	0.171	20 (40.8%)	1.000
Region, n (%)					
North America	102 (58.0%)	19 (19.2%)	<0.001*	3 (6.1%)	<0.001*
Europe	74 (42.0%)	80 (80.8%)	<0.001*	46 (93.9%)	<0.001*
Medical history					
Performance status					
ECOG			0.878		0.124
n (%)	176 (100.0%)	99 (100.0%)	-	49 (100.0%)	-
Mean (SD)	1.2 (0.8)	1.1 (0.8)	-	0.9 (0.5)	-
Median (min, max)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	-	1.0 (0.0, 2.0)	-

Baseline characteristics, unweighted sample[a]	Avapritinib cohort	Midostaurin cohort	p-value (avapritinib vs. midostaurin)[2]	Cladribine cohort	p-value (avapritinib vs. cladribine)[2]
ECOG category, n (%)					
0	36 (20.5%)	19 (19.2%)	0.925	9 (18.4%)	0.904
1	92 (52.3%)	54 (54.5%)	0.813	35 (71.4%)	0.026*
≥2	48 (27.3%)	26 (26.3%)	0.968	5 (10.2%)	0.022*
Anaemia, n (%)	104 (59.1%)	57 (57.6%)	0.907	32 (65.3%)	0.534
Thrombocytopenia, n (%)	67 (38.1%)	56 (56.6%)	0.005*	28 (57.1%)	0.026*
Disease characteristics					
AdvSM subtype diagnosis, n (%)					
SM-AHN	119 (67.6%)	65 (65.7%)	0.843	25 (51.0%)	0.049*
ASM	29 (16.5%)	21 (21.2%)	0.416	17 (34.7%)	0.009*
MCL	28 (15.9%)	13 (13.1%)	0.657	7 (14.3%)	0.957
Any skin involvement, n (%)	58 (33.0%)	30 (30.3%)	0.751	16 (32.7%)	1.000
Leukocyte count ≥16 × 10^9/L, n (%)	33 (18.8%)	23 (23.2%)	0.465	13 (26.5%)	0.320
Serum tryptase ≥125 ng/mL, n (%)	132 (75.0%)	68 (68.7%)	0.324	32 (65.3%)	0.243
KIT mutation					
Patients tested, n (%)	170 (96.6%)	93 (98.9%)	0.428	43 (97.7%)	1.000
KIT D816V positive, n (%)	156 (91.8%)	83 (89.3%)	0.650	39 (90.7%)	0.765
SRSF2/ASXL1/RUNX1 gene panel, n (%)					
Patients tested for ≥1 mutation	176 (100.0%)	78 (83.0%)	<0.001*	40 (90.9%)	0.001*
Number of mutated genes in panel					
0	92 (52.3%)	27 (34.6%)	0.014*	15 (37.5%)	0.131
1	54 (30.7%)	34 (43.6%)	0.064	15 (37.5%)	0.518
≥2	30 (17.1%)	17 (21.8%)	0.469	10 (25.0%)	0.345

Abbreviations: ASM: aggressive systemic mastocytosis; ECOG: Eastern Cooperative Oncology Group; max: maximum; MCL: mast cell leukemia; min: minimum; S/A/R: SRSF2/ASXL1/RUNX1; SD: standard deviation; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm.
Notes: *P<0.05.
[1] The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the midostaurin and cladribine cohorts. Descriptive statistics are reported at the line of therapy level for all variables except KIT and S/A/R mutations, which are reported at the patient level, since each patient in the midostaurin or cladribine cohorts could contribute more than one line of therapy to the analysis.
[2] Comparisons between cohorts were conducted using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables. For categorical variables with expected counts <5, Fisher's exact tests were used instead of Chi-squared.
Source: Reiter et al. (2022)[53]

Table 18. Prior systemic therapy used to treat AdvSM patients (pooled EXPLORER and PATHFINDER, April 2021 data cut-offs)

Prior systemic therapy	Avapritinib cohort	Midostaurin cohort	P-value[1,2] (avapritinib vs. midostaurin)	Cladribine cohort	P-value[1,3] (avapritinib vs. cladribine)
Number of unique patients	N=176	N=94		N=44	
Number of lines of therapy	N=176	N=99		N=49	
Number with prior systemic therapy, n (%)	110 (62.5%)	41 (41.4%)	0.001*	29 (59.2%)	0.798
Prior treatments received,[4] n (%)					
TKI	92 (52.3%)	12 (12.1%)	<0.001*	21 (42.9%)	0.315
Midostaurin	81 (46.0%)	5 (5.1%)	<0.001*	20 (40.8%)	0.627
Dasatinib	6 (3.4%)	4 (4.0%)	0.750	2 (4.1%)	0.686
Imatinib	10 (5.7%)	5 (5.1%)	1.000	2 (4.1%)	1.000
Other[5]	10 (5.7%)	0 (0.0%)	-	0 (0.0%)	-
Cytoreductive therapy	33 (18.8%)	30 (30.3%)	0.042*	11 (22.4%)	0.709
Cladribine	22 (12.5%)	23 (23.2%)	0.032*	5 (10.2%)	0.850
Hydroxyurea	9 (5.1%)	7 (7.1%)	0.691	6 (12.2%)	0.148
Other[5]	7 (4.0%)	2 (2.0%)	0.496	1 (2.0%)	1.000
Biologic therapy	23 (13.1%)	13 (13.1%)	1.000	10 (20.4%)	0.291
Interferon alpha	14 (8.0%)	7 (7.1%)	0.977	8 (16.3%)	0.141
Pegylated interferon	3 (1.7%)	4 (4.0%)	0.256	2 (4.1%)	0.299
Other[5]	4 (2.3%)	2 (2.0%)	1.000	0 (0.0%)	-

*P<0.05. Abbreviations: AdvSM: advanced systemic mastocytosis; max: maximum; min: minimum; SD: standard deviation; TKI: tyrosine kinase inhibitor.
Notes:

[1] Comparisons between cohorts were conducted using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables. For categorical variables with expected counts <5, Fisher's exact tests were used instead of Chi-squared.
[2] Statistical comparisons were conducted between the avapritinib and midostaurin cohorts.
[3] Statistical comparisons were conducted between the avapritinib and cladribine cohorts.
[4] Individual treatments that were observed in ≥4.0% of lines of therapy in any cohort are reported.
[5] Other TKIs included ibrutinib, nilotinib, ripretinib, and ruxolitinib. Other cytoreductive therapies included azacitinide, decitabine, and chlorambucil. Other biologic therapies included brentuximab vedotin, obinituzumab, and rituximab.
Source: Reiter et al (Poster; 2022)[53]

B.2.9.2.3.2 PATHFINDER population (1L/2L+ analysis with updated PATHFINDER 2022 data cut-off)

Baseline characteristics of patients in the 1L/2L+ subgroup analyses based on PATHFINDER 2022, before and after IPTW, are presented in Appendix M, Section M7. It should be noted that

in the analysis comparing 2L+ avapritinib to 2L+ BAT, more patients in the avapritinib cohort had previously received midostaurin than those in the BAT cohort, even after weighting ([redacted]%).[107]

B.2.9.2.4 Overall survival

B.2.9.2.4.1 All-treatment-lines analysis (Pooled EXPLORER and PATHFINDER)

In the unweighted sample, there were 34 (19.3%) deaths among 176 avapritinib patients, 56 (59.6%) among 94 midostaurin patients, and 29 (65.9%) among 44 cladribine patients, with a mean follow-up of 17.9, 27.9, and 24.2 months, respectively (Table 19). Across all lines of therapy, median OS was not reached (95% CI: 46.9, NE) for the avapritinib cohort, 28.6 (18.2, 44.6) months for the midostaurin cohort, and 23.4 (14.8, 40.6) months for the cladribine cohort (Figure 19). In the adjusted analysis after IPTW-weighting, with further adjustment for variables with standardised difference >10% after weighting, avapritinib was still associated with significantly improved OS compared with midostaurin (Table 19).[53]

Table 19. Summary of overall survival (All-treatment-lines analysis)

Overall survival	Avapritinib cohort	Midostaurin cohort	Cladribine cohort
Number of unique patients	**N=176**	**N=94**	**N=44**
Number of lines of therapy	**N=176**	**N=99**	**N=49**
Deaths from unique patients, n (%)	34 (19.3%)	56 (59.6%)	29 (65.9%)
Unique patients censored due to avapritinib initiation, n (%)	--	12 (12.8%)	6 (13.6%)
Unique patients censored due to new primary malignancy after index date, n (%)	--	5 (5.3%)	2 (4.5%)
Mean follow-up (months)	17.9	27.9	24.2
Median OS, unweighted sample (months)	NR	28.6	23.4
(95% CI)	(46.9, NE)	(18.2, 44.6)	(14.8, 40.6)
Avapritinib vs. midostaurin: HR, IPTW-weighted sample (95% CI); p-value[a,b]	0.59 (0.36, 0.97); <0.001*		
Avapritinib vs. cladribine: HR, IPTW-weighted sample (95% CI); p-value[a,b]	0.32 (0.15, 0.67); 0.003*		

Abbreviations:

AdvSM: advanced systemic mastocytosis; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPTW: inverse probability of treatment weighting; OS: overall survival; NE: not estimable; NR: not reached; S/A/R: SRSF2/ASXL1/RUNX1.

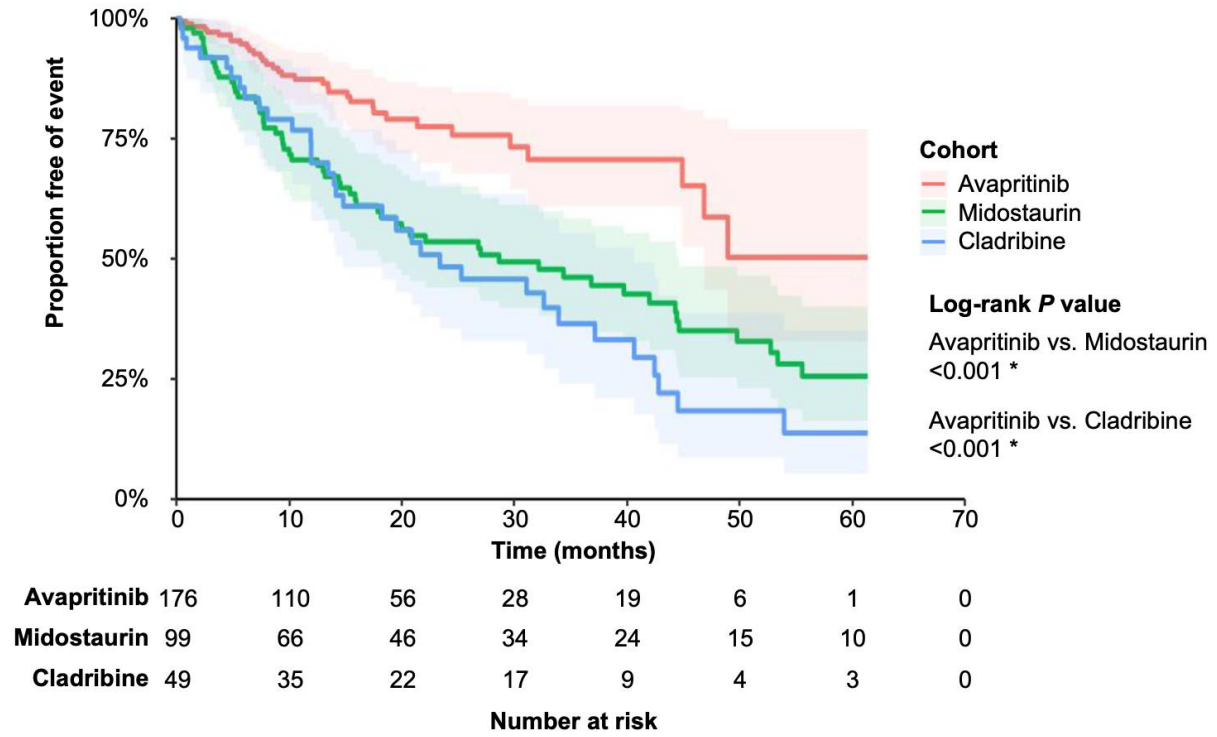
Notes: *p<0.05.

[a] The IPTW-weighted Cox proportional hazards model with a robust sandwich variance estimator was used to model overall survival and further adjusted for covariates with a standardized difference >10% after weighting. HR and the corresponding 95% CI and P value were presented. Two-sided P value <0.05 was considered statistically significant without multiplicity adjustment.

[b] Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anemia (hemoglobin <10 g/dL), thrombocytopenia (platelet count <100 × 109/L), AdvSM subtype, skin involvement, leukocyte count ≥16 × 109/L, serum tryptase level ≥125 ng/mL, number of mutated genes within the S/A/R panel, number of prior lines of

therapy, and prior use of TKI, cytoreductive, and biologic therapy
Source: Reiter et al (Poster; 2022)[53]

Figure 19. Unweighted overall survival for avapritinib vs. midostaurin or cladribine



Abbreviations: AdvSM, advanced systemic mastocytosis; OS, overall survival.
Note: *p<0.05.
Note: The follow-up times for the midostaurin and cladribine cohorts were truncated to match the maximum follow-up time of the avapritinib cohort. In the midostaurin cohort, 94 patients contributed 99 lines of therapy to the analysis. In the cladribine cohort, 44 patients contributed 49 lines of therapy to the analysis.
Source: Reiter et al (Poster; 2022)[53]

B.2.9.2.4.2 1L/2L+ analysis (updated PATHFINDER population)

In the analysis comparing patients who received 1L 200 mg avapritinib in PATHFINDER (2022 data cut-off) to 1L midostaurin patients, after weighting, 1L avapritinib was associated with significantly improved OS vs. 1L midostaurin (HR [95% CI]: 0.13 [0.04, 0.42]; p<0.001 and [redacted], RAC-RE and safety populations respectively) (Table 20**,** Figure 20**)**.[106]

When comparing patients who received 2L+ avapritinib 200 mg in the updated PATHFINDER populations to real-world patients who received 2L+ cladribine, results were similar to the pooled analysis, however with borderline statistical significance. After weighting, 2L+ avapritinib 200 mg was associated with numerically, but not significantly, improved OS compared with 2L+ cladribine (Table 20**,** Figure 21**)**.[108]

Statistically significant improvements in OS were demonstrated when comparing 2L+ avapritinib (PATHFINDER 2022 data cut-off) to 2L+ BAT (HR [95% CI]: [redacted] and [redacted], RAC-RE and safety populations respectively; Table 20, Figure 22).[107]

Figure 20. Weighted Kaplan-Meier curves for overall survival for subgroup analysis: 1L avapritinib PATHFINDER (safety population and RAC-RE Population) vs. 1L Midostaurin

Abbreviations: 1L, first line of therapy; OS, overall survival; RAC-RE, response evaluation committee response-evaluable
Source: External Control Study: Analysis of 1L avapritinib and 1L midostaurin (PATHFINDER 2022 data cut-off) [Data on file][106]

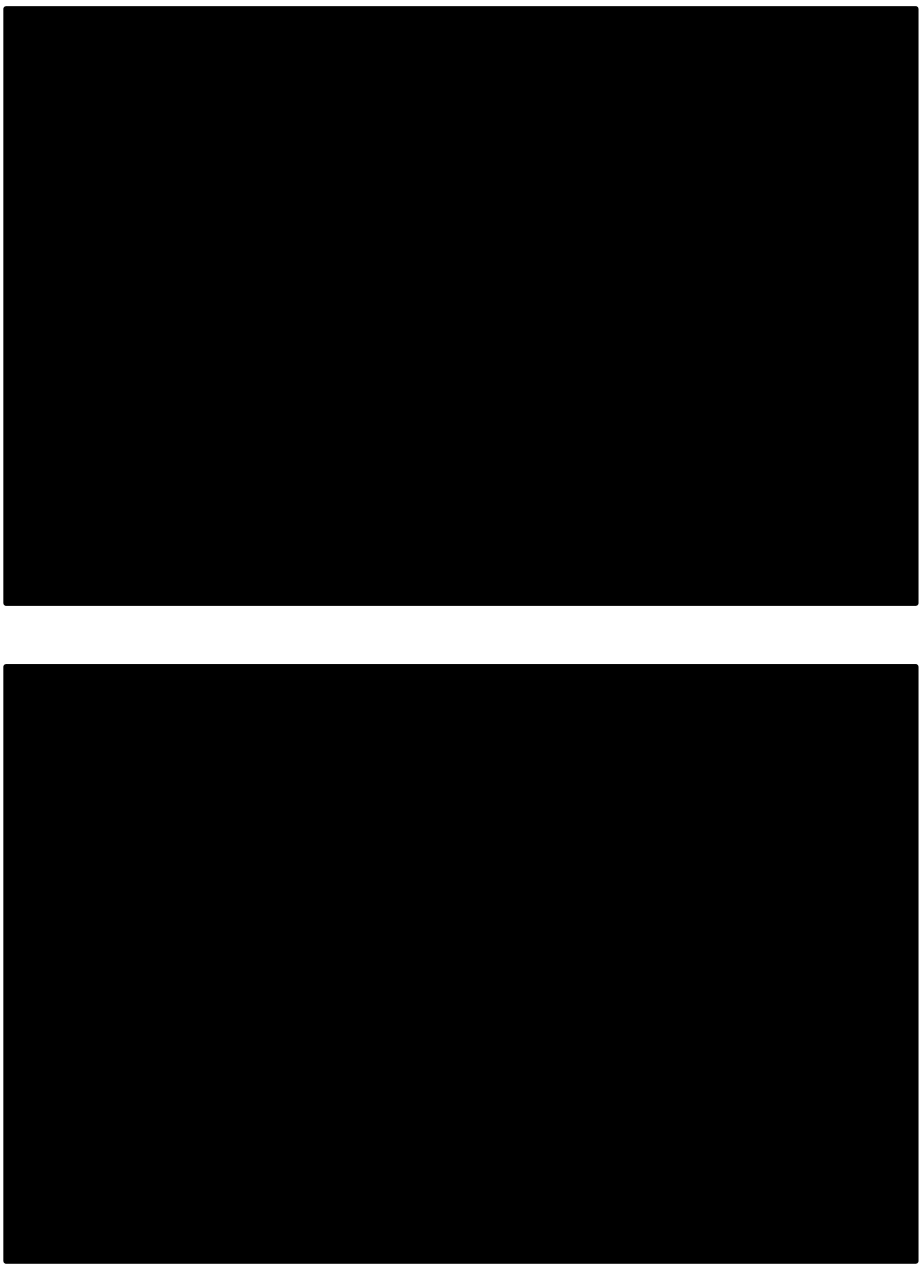
Figure 21. Weighted Kaplan-Meier curves for overall survival for subgroup analysis: 2L+ avapritinib PATHFINDER (safety population and RAC-RE Population) vs. 2L+ cladribine

Abbreviations: 2L+, second or later line of therapy; OS, overall survival; RAC-RE, response evaluation committee response-evaluable

Note: The number at risk are based on the unweighted analysis sets, as for the weighted analyses the statistical software (R) features the sum of the weights instead of the number of patients at risk.

Source: External Control Study: Analysis of 2L+ avapritinib and 2L+ cladribine (PATHFINDER 2022 data cut-off) [Data on file][108]

Figure 22. Weighted Kaplan-Meier curves for overall survival for subgroup analysis: 2L+ avapritinib PATHFINDER (safety population and RAC-RE Population) vs. 2L+ BAT



Abbreviations: 2L+, second or later line of therapy; OS, overall survival; RAC-RE, response evaluation committee response-evaluable

Note: The number at risk are based on the unweighted analysis sets, as for the weighted analyses the statistical software (R) features the sum of the weights instead of the number of patients at risk.

Source: External Control Study: Analysis of 2L+ avapritinib and 2L+ BAT (PATHFINDER 2022 data cut-off) [Data on file][107]

Table 20. Summary of overall survival (1L/2L+ analysis)

Study sample	Unweighted sample				IPTW-weighted sample			
	Avapritinib cohort	Mido, Clad or BAT	Estimate (95% CI)	*P*-value	Avapritinib cohort	Mido, Clad or BAT	Estimate (95% CI)	*P*-value
Avapritinib 1L (200 mg PATHFINDER RAC-RE population) vs. Mido-1L[a,c]								
Number of lines of therapy (number of unique patients)	30 (30)	58 (58)			31 (31)	58 (58)		
Mean follow-up (months)	[redacted]	[redacted]			[redacted]	[redacted]		
Median OS (months) (95% CI)[b]	NR (NE, NE)	28.6 (18.2, 49.8)			NR (NE, NE)	32.2 (22.1, 44.6)	--	--
HR (95% CI)	--	--	0.17 (0.05, 0.54)	0.003*	--	--	0.13 (0.04, 0.42)	<0.001 *
Avapritinib 1L (200 mg PATHFINDER Safety population) vs. Mido-1L [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]			[redacted]	[redacted]		
Mean follow-up (months)	[redacted]	[redacted]			[redacted]	[redacted]		
Median OS (months)	[redacted]	[redacted]	--	--	[redacted]	[redacted]		
(95% CI)[b]	[redacted]	[redacted]			[redacted]	[redacted]		
HR (95% CI)	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Avapritinib 2L+ (200 mg PATHFINDER RAC-RE population) vs. Clad-2L+ [a,c]								
Number of lines of therapy (number of unique patients)	51 (51)	29 (27)	--	--	56 (56)	24 (23)	--	--
Mean follow-up (months)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median OS (months) (95% CI)[b]	NR (NE, NE)	21.7 (14.0, 42.4)	--	--	NR (NE, NE)	21.7 (14.0, 42.8)	--	--
HR (95% CI)	--	--	0.37 (0.19, 0.73)	0.004*	--	--	0.34 (0.12, 1.02)	0.054
Avapritinib 2L+ (200 mg PATHFINDER safety population) vs. Clad- 2L+[a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Mean follow-up (months)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median OS (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]

Study sample	Unweighted sample				IPTW-weighted sample			
	Avapritinib cohort	Mido, Clad or BAT	Estimate (95% CI)	*P*-value	Avapritinib cohort	Mido, Clad or BAT	Estimate (95% CI)	*P*-value
Avapritinib 2L+ (200 mg PATHFINDER RAC-RE population) vs. BAT-2L+ [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Mean follow-up (months)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median OS (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Avapritinib 2L+ (200 mg PATHFINDER safety population) vs. BAT- 2L+[a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Mean follow-up (months)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median OS (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)	--		[redacted]	[redacted]	--		[redacted]	[redacted]

*p<0.05. Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NA, not available; NE, not estimable; NR, not reached; OS, overall survival.
Notes: [a] Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference >10% after weighting
[b] Median overall survival was estimated using the Kaplan-Meier method.
[c] Data from PATHFINDER (data cut-off date of September 09, 2022) were used.
Source: ECS analysis 1L mido (data on file),[106] ECS analysis 2L+ cladribine (data on file),[108] ECS analysis 2L+ BAT (data on file).[107]

B.2.9.2.5 Duration of treatment

B.2.9.2.5.1 1L/2L+ analysis (Updated PATHFINDER population)

In the updated PATHFINDER analysis, after weighting, 1L avapritinib was associated with significantly longer DOT than 1L midostaurin (HR [95% CI]: 0.26 [0.13, 0.53]; *p*<0.001 and [redacted], RAC-RE and safety populations respectively).[106]

After weighting, 2L+ avapritinib 200 mg was also associated with significantly longer DOT:

- compared with 2L+ cladribine (HR [95% CI]: 0.13 [0.06, 0.27]; p<0.001 and [redacted], RAC-RE and safety populations respectively).[108]
- compared with 2L+ BAT (HR [95% CI]: [redacted] and [redacted], RAC-RE and safety populations respectively); Table 21).[107]

Table 21. Summary of duration of therapy (1L/2L+ analysis)

	Unweighted sample				IPTW-Weighted sample[2]			
	Avapritinib	**Mido clad or BAT**	**Estimate (95% CI)**	***P*-value**	**Avapritinib**	**Mido clad or BAT**	**Estimate (95% CI)**	***P*-value**
Avapritinib 1L (200 mg PATHFINDER RAC-RE population) vs. Mido-1L[a,c]								
Number of lines of therapy (number of unique patients)	30 (30)	58 (58)	--	--	31 (31)	58 (58)	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI)[b]	41.3 (33.9, NE)	11.6 (7.5, 22.1)	--	--	41.3 (33.9, 41.3)	13.0 (7.9, 25.5)	--	--
HR (95% CI)	--	--	0.23 (0.11, 0.46)	<0.001 *			0.26 (0.13, 0.53)	<0.001 *
Avapritinib 1L (200 mg PATHFINDER Safety population) vs. Mido-1L [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Avapritinib 2L+ (200 mg PATHFINDER RAC-RE population) vs. Clad-2L+ [a,c]								
Number of lines of therapy (number of unique patients)	51 (51)	25 (24)	--	--	54 (54)	21 (21)	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI)[b]	NR (18.3, NE)	4.7 (2.7, 8.1)	--	--	NR (17.1, NE)	4.7 (2.1, 5.4)	--	--
HR (95% CI)[4]	--	--	0.19 (0.11, 0.34)	<0.001 *	--	--	0.13 (0.06, 0.27)	<0.001 *

	Unweighted sample				IPTW-Weighted sample[2]			
	Avapritinib	**Mido clad or BAT**	**Estimate (95% CI)**	***P*-value**	**Avapritinib**	**Mido clad or BAT**	**Estimate (95% CI)**	***P*-value**
Avapritinib 2L+ (200 mg PATHFINDER safety population) vs. Clad- 2L+ [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI) [b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Avapritinib 2L+ (200 mg PATHFINDER RAC-RE population) vs. BAT-2L+ [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)[4]	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Avapritinib 2L+ (200 mg PATHFINDER safety population) vs. BAT- 2L+ [a,c]								
Number of lines of therapy (number of unique patients)	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Number of discontinued lines of therapy	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
Median DOT (months) (95% CI)[b]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	--	--
HR (95% CI)[4]	--	--	[redacted]	[redacted]	--	--	[redacted]	[redacted]

*p<0.05. Abbreviations**:** 1L, first line of therapy; 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; CI, confidence interval; DOT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable.

Notes**:**

[a] Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference >10% after weighting

[b] Median duration of treatment was estimated using the Kaplan-Meier method
[c] Data from PATHFINDER (data cut-off date of September 09, 2022) were used
Source: ECS analysis 1L mido (data on file),[106] ECS analysis 2L+ cladribine (data on file),[108] ECS analysis 2L+ BAT (data on file).[107]

B.2.9.3 MAIC against midostaurin clinical studies

B.2.9.3.1 Methodology

Detailed methodology of the MAIC analyses (published by Pilkington et al., 2022)[52] is provided in Appendix D. In brief, an SLR identified two pivotal trials for avapritinib (EXPLORER and PATHFINDER) and two pivotal trials for midostaurin (D2201 and A2213, summarised in Table 22). Unanchored MAIC and/or naïve ITCs were used to compare the relative efficacy of avapritinib with midostaurin in terms of OS, ORR, and CR. For MAIC of OS, age, AdvSM type, and race were matched for analyses, while for ORR and CR, additionally matched variables included ECOG performance status, the presence of a *KIT* D816V mutation, bone marrow mast cell burden, and prior systemic therapy.[52] In addition to the primary comparison of pooled data from both available trials for midostaurin and avapritinib, a number of sensitivity analyses of different patient populations were also performed from these data.

The avapritinib studies have been described in Sections 2.2 to 2.4. A summary of the included midostaurin studies is shown in Table 22. The midostaurin studies are the same as those presented during the midostaurin NICE assessment (TA728).

Table 22. Midostaurin studies included in the MAIC

Study name Trial name (NCT)	Study phase	Study design Blinding	Study setting Study country	Intervention/ comparator	Primary outcome Secondary outcome	Length of follow-up Median Mean
Gotlib et al., 2016[69] CPKC412**D2201** (NCT00782067)	Phase 2	• Single arm • Open label	• Multicentre • United States, Australia, Austria, Belgium, Canada, France, Germany, Netherlands, Norway, Poland, Turkey, United Kingdom	• Midostaurin	• Best overall response • OS, PFS, DOR, safety, toxic effects, patient-reported symptoms and QoL	• 30.5-month • NR
DeAngelo et al., 2018[110] PKC412**A2213** (NCT00233454)	Phase 2	• Single arm • Open label	• Multicentre • United States	• Midostaurin	• ORR • Secondary outcome: safety and tolerability, evaluation of the *KIT* mutation status and OS and PFS	• 124 months (range 82-140 months) • NR

B.2.9.3.2 Baseline characteristics

All four studies were open-label, single-arm trials and had similar inclusion/exclusion criteria in terms of age, disease subgroups enrolled and ECOG performance status. In general, the

baseline characteristics of patients were relatively comparable across the four efficacy populations in the studies. The comparability of baseline characteristics at treatment level supported the decision to pool data across the midostaurin and avapritinib evidence, when possible.[52]

Differences in characteristics across the studies were noted for ECOG performance status, prior therapy, serum tryptase levels and *KIT* D816V mutation status. A2213 included more patients with ECOG performance status 2/3 than the other three studies. EXPLORER, PATHFINDER and A2213 included more patients who had received prior therapy compared with D2201. Medium serum tryptase levels ranged from 182 to 323 µg/l across the four studies (levels were lowest in EXPLORER and highest in A2213). More patients in the avapritinib populations had a positive *KIT* D816V mutation status than in the midostaurin populations.[52]

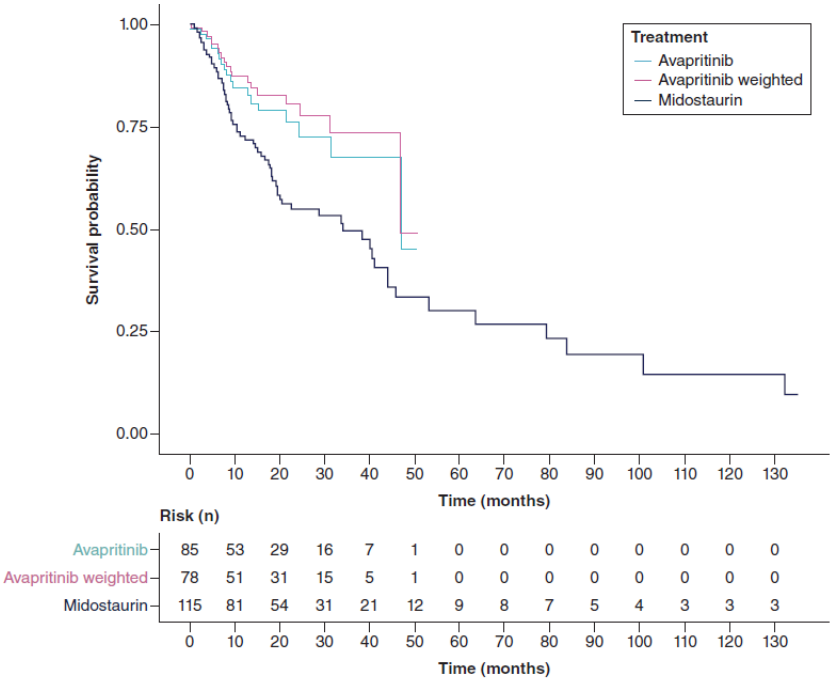
Differences in the number of C-findings per patient were also noted. However, due to the evolving definition of C-findings between the earlier and later studies and the counting principle for the number of C-findings per patient, the authors deemed it inappropriate to draw conclusions about the comparability of the number of C-findings per patient across the avapritinib and midostaurin studies.

B.2.9.3.3 Relative efficacy of avapritinib and midostaurin on OS

Estimates of OS comparisons demonstrate avapritinib to consistently be associated with a reduction in the risk of death, with HRs ranging from 0.37 to 0.67. Sensitivity analyses were relatively consistent with the primary analysis. Using data from PATHFINDER as the avapritinib evidence or a subgroup of patients who received the 200 mg starting dose in pooled EXPLORER and PATHFINDER data produced slightly higher MAIC HRs than the primary analysis.[52]

The Kaplan-Meier OS plot (Figure 23) demonstrates the enhanced survival probability for patients receiving avapritinib, which becomes more pronounced when the avapritinib population is weighted to more closely resemble the midostaurin population.

Figure 23. Kaplan-Meier plot of OS for avapritinib and midostaurin

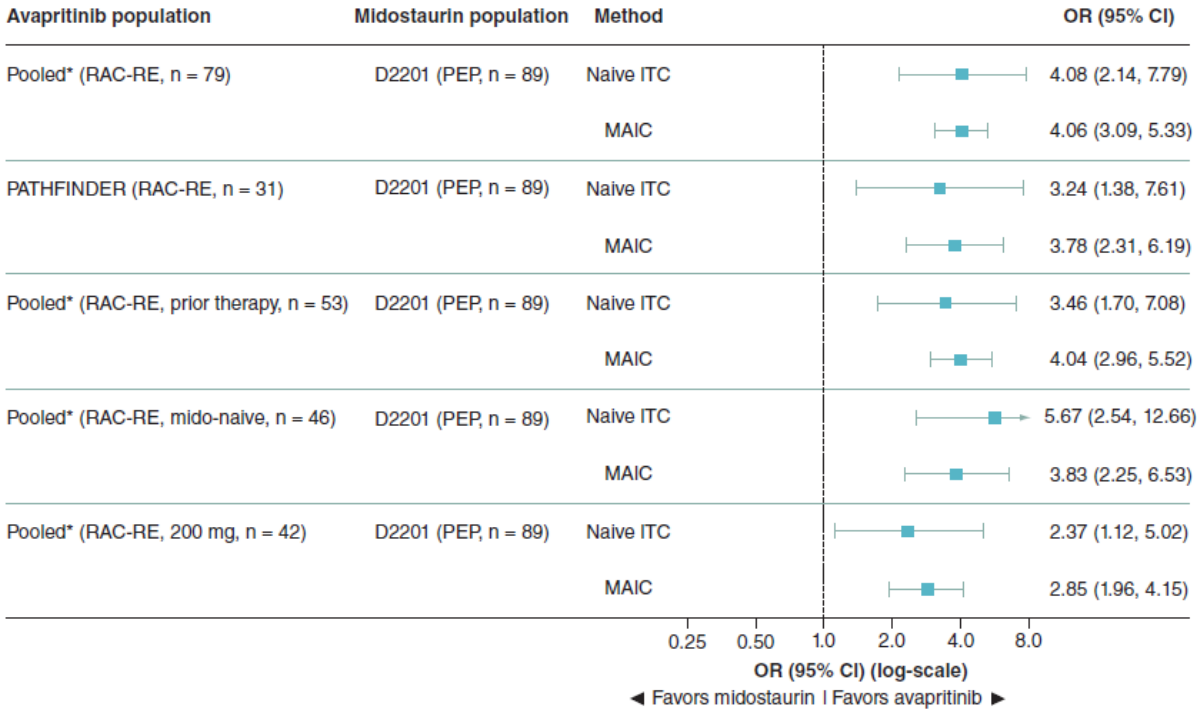


Abbreviations: AdvSM, advanced systemic mastocytosis; OS, overall survival. Note: population assesed for avapritinib = pooled response assessment committee response-evaluable population; population assessed for midostaurin = pooled primary efficacy population. The weighted analysis adjusted the avapritnib population for age, AdvSM subtype, and race. Source: Pilkington at al. 2022[52]

B.2.9.3.4 Relative efficacy of avapritinib and midostaurin on ORR

To assess ORR between avapritinib and midostaurin, IWG-MRT-ECNM criteria were used (ORR=CR+PR+CI), as this was a common assessment shared between studies of both therapies. While both EXPLORER and PATHFINDER included IWG-MRT-ECNM criteria as sensitivity analyses (primary analysis of ORR was based on mIWG-MRT-ECNM criteria), only study D2201 for midostaurin used this criterion in post hoc analyses.[60] ORRs of 69.62% and 35.95% were seen for avapritinib and midostaurin, respectively (pooled PATHFINDER and EXPLORER, RAC-RE, n-79). In line with the almost doubled ORR for avapritinib, odds ratios (ORs) in Figure 24 show that patients treated with avapritinib were 2.37–5.67 times more likely to achieve a best response (CR+PR+CI) compared to midostaurin.

Figure 24: Odds ratios comparing ORR between avapritinib and midostaurin

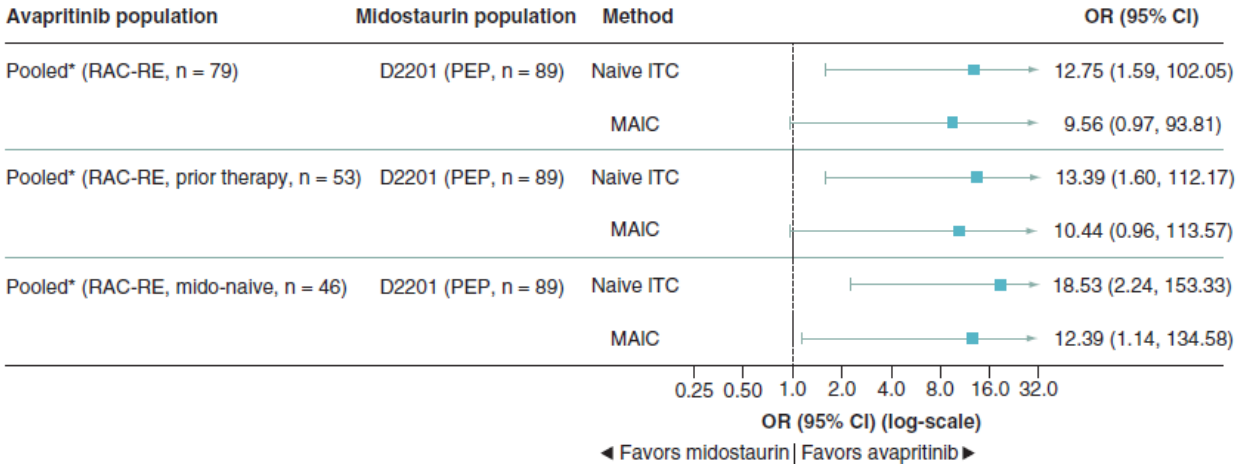


Abbreviations: AdvSM, advanced systemic mastocytosis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MAIC, matching-adjusted indirect comparison; mido, midostaurin; OR, odds ratio; ORR, overall response rate; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable. *Pooled EXPLORER and PATHFINDER population. Note the MAIC analyses weighted the avapritnib population for age, AdvSM subtype, race, ECOG status, presence of *KIT* D816V mutation, bone marrow mast cell burden, and prior systemic therapy.
Source: Pilkington at al. 2022[52]

B.2.9.3.5 Relative efficacy of avapritinib and midostaurin on CR

Rates of CR were also higher for avapritinib compared to midostaurin (12.66% vs. 1.12%; Pooled PATHFINDER and EXPLORER (RAC-RE), n=79). Patients treated with avapritinib demonstrated likelihoods of CR of 9.56–18.53 higher compared to midostaurin (Figure 25). Due to the low number of CR events (only one patient for midostaurin), the CIs for ORs of CR were elevated.

Figure 25: Odds ratios comparing CR for avapritinib and midostaurin



Abbreviations: AdvSM, advanced systemic mastocytosis; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MAIC, matching-adjusted indirect comparison; mido, midostaurin; OR, odds ratio; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable. *Pooled EXPLORER and PATHFINDER population. Note: Note the MAIC analyses weighted the avapritnib population for age, AdvSM subtype, race, ECOG status, presence of *KIT* D816V mutation, bone marrow mast cell burden, and prior systemic therapy.
Source: Pilkington at al. 2022[52]

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

B.2.9.4.1 External control study

This study benefited from several strengths related to its methodology and employed strategies to maximise comparability between the two cohorts and reduce uncertainty in the estimates of comparative efficacy. These included using:[7]

- Eligibility criteria for the BAT cohort similar to those of the EXPLORER and PATHFINDER trials
- A standardised procedure for data collection across study sites
- Harmonisation of definitions for the outcomes and key baseline characteristics between the two treatment cohorts
- Rigorous statistical methods (IPTW-weighting and doubly robust estimation) to account for the potential differences in the comprehensive list of a priori specified key adjustment covariates between the avapritinib and BAT cohorts.

Data were collected from patients treated at centres of excellence between 2009 and 2021 and are therefore expected to be representative of current clinical practice.

The study has some limitations that should be taken into account when interpreting the data:[7]

- AdvSM diagnosis information was based on local clinician-assessed evaluation using the 2016 revision to the WHO diagnostic criteria, and correct diagnosis might not always have been made and correct diagnosis might not have been made prior to the substantial increases in disease awareness and knowledge occurring in the last decade. AdvSM diagnoses for the avapritinib cohort were based on the same criteria but confirmed by the RAC. Thus, there may have been misclassification of the clinician-assessed AdvSM diagnosis in the BAT cohort, which could result in an underestimation of the difference in OS (OS for patients with indolent SM and smouldering SM is typically longer than for patients with AdvSM). However, as all participating sites are centres with expertise in the treatment of AdvSM, this concern is mitigated.
- Comparison of response rates and AEs was not possible.
- Due to the retrospective nature of data collection for the BAT cohort, the results may have been impacted by incomplete reporting for key prognostic factors, such as performance status. However, a sensitivity analysis assessing the impact of missing performance status indicated that this is not expected to impact the results.
- In the primary analysis of OS, 15% of patients from the BAT cohort went on to receive avapritinib as part of EXPLORER or PATHFINDER. These patients were included in the BAT cohort and censored at the initiation of avapritinib. Because no identifiable information was collected for real-world patients, some of these patients may have been included in the avapritinib cohort as well.

B.2.9.4.2 MAIC

Based on comparisons of avapritinib and midostaurin from four prospective clinical trials, clear benefit was demonstrated for avapritinib when considering efficacy in patients with AdvSM. Results of the analysis demonstrated that avapritinib produced higher likelihoods of survival and achieving a response to treatment, including CR, and this occurred when comparing the midostaurin-naïve subgroup of the avapritinib cohort and in the analyses of patients who had previously received systemic therapy.

The analysis has the following limitations:[52]

- The main assumption required to be able to perform unanchored MAIC analyses is that there are no unmeasured prognostic factors or treatment effect modifiers in imbalance between the two populations being compared. Only aggregate data was available for the midostaurin studies and there were potential cross-trial differences in prognostic factors. Moreover, because the trials are single-arm trials it is unknown whether there were any underlying treatment effect modifiers that needed to be accounted for. The potential omission of prognostic factors and treatment effect modifiers can introduce bias into the results.
- Assessment of response differed between the studies, and only one of the midostaurin studies included the IWG-MRT-ECNM criteria in a post hoc analysis.

- The analysis was carried out using avapritinib study data cut-offs from 2021, and length of follow-up was considerably shorter in the avapritinib trials (50 months) than the midostaurin trials (more than 120 months).
- Due to the rarity of AdvSM, sample sizes across the four included studies were small, which could lead to increased uncertainty. Pooling data could provide another source of uncertainty as the studies have different study protocols and median follow-up durations. Pooling also removes the opportunity to capture differences between trials. The sensitivity analyses that only used data from PATHFINDER were consistent with the primary analyses, demonstrating that pooling likely did not have a considerable impact on the results.
- The outcome of CR was affected by the small sample sizes of the studies and very small numbers of events observed.
- There were differences in the doses of avapritinib used in the avapritinib studies as the EXPLORER trial was a dose-finding study. The patients who received a 200 mg starting dose (the recommended starting dose) had the shortest follow-up. However, the EXPLORER trial has demonstrated that responses to avapritinib deepen over time. This is likely why the 200 mg subgroup sensitivity analyses demonstrated slightly reduced efficacy compared with the full population.
- The midostaurin trials were conducted earlier in time (2006 and 2009) compared with the avapritinib trials (2016 and 2018) therefore changes in the standard of care could make midostaurin appear comparatively less effective than avapritinib.
- It was not possible to perform comparisons with the subgroup of midostaurin patients who received prior systemic therapy, because results for this subgroup were not available; therefore, it was assumed that the treatment effect was comparable for patients who received and did not receive prior systemic therapy in the midostaurin population.

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.

This section outlines the adverse event data reported in PATHFINDER (September 2022 data cut-off used in the economic modelling) to demonstrate the safety of avapritinib in patients with AdvSM.

Additionally, the following sources provide evidence for the safety of avapritinib:

- An analysis of safety data for the EXPLORER as of the April 2022 data cut-off have been reported by DeAngelo et al., 2022.[76] These data are from patients with starting doses of

avapritinib ranging from 30–400 mg OD and included treatment-related AEs. These data are not used in the economic model and are presented in Appendix M, Section M3.

- Pooled safety data from the PATHFINDER and EXPLORER studies (April 2021 data cut-off for both studies) have been provided during regulatory submission to the MHRA. These data are not used in the economic model and are presented in Appendix M, Section M6.
- An overview of adverse reactions as reported in the safety database as of the April 2021 data cut-off is provided in the draft UK SmPC (Appendix C).

B.2.10.1 Overall summary of adverse events

As of the September 2022 data cut-off, in patients treated with a 200 mg avapritinib starting dose in PATHFINDER, mean treatment durations are 20.7 months (SD: 12.3) in patients with prior systemic therapy and 23.5 months (SD: 10.9) in patients without prior systemic therapy.

An overall summary of AEs in patients who initiated avapritinib at 200 mg in PATHFINDER is provided in Table 23. All patients experienced at least one AE; 50.5% of patients experienced a serious AE, 82.9% of patients experienced an AE of grade 3 severity or worse, and 23.8% of patients had an AE that led to discontinuation from PATHFINDER. Treatment-related AEs, as assessed by the Investigators, occurred in 96.2% of patients; only 14.3% of patients experienced serious treatment-related AEs, 63.8% of patients experienced treatment-related AEs of grade 3 severity or worse, and 10.5% of patients experienced treatment-related AEs that led to discontinuation of study drug.

As of the data cut-off, 69.5% of patients had a dose interruption and 77.1% of patients had an AE that led to dose reduction. The median average daily dose of avapritinib as of the data cut-off in patients who initiated avapritinib at a dose of 200 mg is 119.0 mg (range: 29.0, 240.0) in patients who had received prior systemic therapy and 102.5 mg (range: 53.0, 200.0) in patients who had not received prior systemic therapy.

Adverse events of special interest (AESIs) included cognitive effects and intracranial bleeding. As of the data cut-off, cognitive effects considered to be an AESI were reported in 29 patients (27.6%; assessed as related to treatment in 26 [24.8%] patients) and intracranial bleeding events considered to be an AESI were reported in 4 patients (3.7%), all of which were assessed as related to treatment. All patients who experienced intracranial bleeding discontinued treatment.

Table 23. Overall summary of AEs (PATHFINDER, safety population, 200 mg avapritinib starting dose, September 2022 data cut-off)

Category	Proportion of safety population (n=105) n (%)
Any AE	105 (100.0)

Category	Proportion of safety population (n=105) n (%)
Serious AE	53 (50.5)
Grade 3+ AE	87 (82.9)
Treatment-related AE	101 (96.2)
Serious treatment-related AE	15 (14.3)
Grade 3+ treatment-related AE	67 (63.8)
AE leading to discontinuation from study drug	25 (23.8)
Patients with treatment-related AE leading to discontinuation from study drug	11 (10.5)
Patients with AE leading to dose interruption	73 (69.5)
Patients with AE leading to dose reduction	81 (77.1)

Abbreviations: AE, adverse event; AESI, adverse event of special interest. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.10.2 Common adverse events

A summary of AEs by system organ class and preferred term is provided in Table 24. All AEs that occurred in ≥10% of all patients and all AEs of Grade 3 or higher that occurred in ≥2% of patients are listed. Fatal AEs occurred in 9 patients, including intra-abdominal haemorrhage, necrotising fasciitis, acute kidney injury, acute hepatic failure, endocarditis, sepsis, haemorrhagic shock, *Escherichia* sepsis, disease progression, pneumonia aspiration, and erosive gastritis. No fatal AEs were related to treatment.

Table 24. Summary of AEs in ≥10% of patients and Grade ≥3 AEs in ≥2% of patients by system organ class and preferred term (PATHFINDER, safety population, 200 mg avapritinib, September 2022 data cut-off)

Category	Proportion of safety population (n=105) n (%)	
	AEs	Grade ≥3 AEs
Blood and lymphatic system disorders	**82 (78.1)**	**48 (45.7)**
Anaemia	54 (51.4)	28 (26.7)
Thrombocytopenia	45 (42.9)	20 (19.0)
Neutropenia	24 (22.9)	21 (20.0)
Eye disorders	**69 (65.7)**	**8 (7.6)**
Periorbital oedema	43 (41.0)	6 (5.7)
Eyelid oedema	18 (17.1)	0
Gastrointestinal disorders	**85 (81.0)**	**20 (19.0)**
Diarrhoea	33 (31.4)	5 (4.8)
Nausea	25 (23.8)	1 (1.0)
Vomiting	21 (20.0)	2 (1.9)
Constipation	15 (14.3)	0
Abdominal pain	13 (12.4)	1 (1.0)

Category	Proportion of safety population (n=105) n (%)	
	AEs	Grade ≥3 AEs
General disorders and administration site conditions	**74 (70.5)**	**11 (10.5)**
Oedema peripheral	49 (46.7)	2 (1.9)
Fatigue	20 (19.0)	3 (2.9)
Face oedema	17 (16.2)	0
Asthenia	11 (10.5)	2 (1.9)
Infections and infestations	**65 (61.9)**	**22 (21.0)**
Corona virus infection	13 (12.4)	3 (2.9)
Investigations	**71 (67.6)**	**35 (33.3)**
Blood alkaline phosphatase increased	16 (15.2)	4 (3.8)
Blood bilirubin increased	16 (15.2)	4 (3.8)
Neutrophil count decreased	14 (13.3)	11 (10.5)
Weight increased	14 (13.3)	4 (3.8)
Blood creatinine increased	13 (12.4)	0
Platelet count decreased	12 (11.4)	8 (7.6)
White blood cell count decreased	12 (11.4)	7 (6.7)
Gamma-glutamyl transferase increased	8 (7.6)	3 (2.9)
Metabolism and nutrition disorders	**47 (44.8)**	**8 (7.6)**
Hyperuricaemia	13 (12.4)	0
Hypokalaemia	8 (7.6)	3 (2.9)
Musculoskeletal and connective tissue disorders	**48 (45.7)**	**3 (2.9)**
Arthralgia	18 (17.1)	0
Pain in extremity	12 (11.4)	0
Nervous system disorders	**62 (59.0)**	**7 (6.7)**
Cognitive disorder	18 (17.1)	3 (2.9)
Dysgeusia	18 (17.1)	0
Headache	14 (13.3)	0
Dizziness	10 (9.5)	0
Renal and urinary disorders	**17 (16.2)**	**9 (8.6)**
Renal failure	5 (4.8)	3 (2.9)
Chronic kidney disease	4 (3.8)	3 (2.9)
Respiratory, thoracic, and mediastinal disorders	**42 (40.0)**	**8 (7.6)**
Epistaxis	14 (13.3)	0
Dyspnoea	12 (11.4)	3 (2.9)
Skin and subcutaneous tissue disorders	**59 (56.2)**	**2 (1.9)**
Hair colour changes	17 (16.2)	0
Pruritus	14 (13.3)	0
Rash	14 (13.3)	1 (1.0)
Alopecia	12 (11.4)	0
Vascular disorders	**23 (21.9)**	**6 (5.7)**
Hypertension	7 (6.7)	3 (2.9)

Abbreviations: AE, adverse event. Note: AEs are presented by system organ class (bold) or preferred term if an AE by preferred term occurred in ≥10% of patients. All AEs of Grade 3 or greater that occurred in ≥2% of patients are

additionally reported. Grades of severity for AEs are defined by the National Cancer Institute Common Terminology Criteria for Adverse Events. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.10.3 Treatment-related adverse events

A summary of treatment-related AEs by system organ class and preferred term is provided in Table 25. All treatment-related AEs that occurred in ≥10% of all patients and all treatment-related AEs of Grade 3 or higher that occurred in ≥2% of patients are reported.

Table 25. Summary of treatment-related AEs in ≥10% of patients and Grade ≥3 treatment-related AEs in ≥2% of patients by system organ class and preferred term (PATHFINDER, safety population, 200 mg avapritinib starting dose, September 2022 data cut-off)

Category	Proportion of safety population (n=105) n (%)	
	AEs	Grade ≥3 AEs
Blood and lymphatic system disorders	**66 (62.9)**	**38 (36.2)**
Thrombocytopenia	42 (40.0)	19 (18.1)
Anaemia	31 (29.5)	14 (13.3)
Neutropenia	19 (18.1)	17 (16.2)
Eye disorders	**64 (61.0)**	**7 (6.7)**
Periorbital oedema	42 (40.0)	6 (5.7)
Eyelid oedema	18 (17.1)	0
Gastrointestinal disorders	**41 (39.0)**	**3 (2.9)**
Diarrhoea	15 (14.3)	1 (1.0)
Nausea	11 (10.5)	0
General disorders and administration site conditions	**63 (60.0)**	**6 (5.7)**
Oedema peripheral	41 (39.0)	2 (1.9)
Face oedema	16 (15.2)	0
Fatigue	12 (11.4)	2 (1.9)
Investigations	**48 (45.7)**	**24 (22.9)**
Neutrophil count decreased	11 (10.5)	9 (8.6)
Platelet count decreased	11 (10.5)	8 (7.6)
White blood cell count decreased	11 (10.5)	7 (6.7)
Blood bilirubin increased	8 (7.6)	3 (2.9)
Nervous system disorders	**47 (44.8)**	**3 (2.9)**
Cognitive disorder	17 (16.2)	3 (2.9)
Dysgeusia	17 (16.2)	0
Skin and subcutaneous tissue disorders	**37 (35.2)**	**1 (1.0)**
Hair colour changes	17 (16.2)	0
Alopecia	11 (10.5)	0

Abbreviations: AE, adverse event. Note: Treatment-related AEs are presented by system organ class (bold) or preferred term if a treatment-related AE by preferred term occurred in ≥10% of patients. All treatment-related AEs of Grade 3 or greater that occurred in ≥2% of patients are additionally reported. Grades of severity for AEs are defined by the National

Cancer Institute Common Terminology Criteria for Adverse Events. The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[72]

B.2.11 Ongoing studies

The PATHFINDER study is ongoing, with expected completion in January 2026. Results from the latest data cut-off (September 2023) are expected to be available in Q2 2024. Available and planned data cut-offs are shown in Table 6.

The EXPLORER study completed in April 2023 with the final CSR completed in January 2024. Although it was not possible to incorporate the results into this submission, the final CSR has been provided.[101]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Key findings

In the PATHFINDER clinical trial, avapritinib demonstrated efficacy in treating patients with AdvSM (ASM, SM-AHN, and MCL); avapritinib induced sustained clinically meaningful improvements across measures of mast cell burden, disease-related symptoms, and daily functioning (HRQoL). Key efficacy results were consistent in EXPLORER and PATHFINDER, providing evidence of meaningful clinical benefit.[75,76]

Treatment with avapritinib at a starting dose of 200 mg OD produced rapid, deep and durable responses in PATHFINDER based on assessment using the best currently available set of response criteria, the mIWG-MRT-ECNM criteria.[73,76] Two patients who received 100 mg as an initial dose in PATHFINDER were included in the response-evaluable population. In order to fully reflect the expected UK licensed dose, analysis of PATHFINDER data excluding these two patients has been presented and is included in the economic modelling. In patients treated with avapritinib at a starting dose of 200 mg OD the ORR was 74.1% (95% CI: 63.1, 83.2), A significant proportion of patients treated with avapritinib at a starting dose of 200 mg OD achieved CR or CRh: CR/CRh was seen for 27% (n=22/81) of all patients in PATHFINDER, 40% (n=12/30) of treatment-naïve patients and 20% of patients who previously received one or more systemic therapies (n=5/51).[72] Considering the lack of CR observed in midostaurin studies,[69] this rate of CR/CRh is unprecedented and provides the opportunity for further curative treatment with allo-HSCT.

Time to response was rapid, occurring in most patients in under three months: in PATHFINDER median time to response was 2.2 months (range: 0.3 to 15 months) and median time to CR or CRh was 9.1 months (range 1.8 to 26 months). As of the latest data cut-offs (April 2022 and September 2022), there have been few losses of response. In PATHFINDER, 52/60 (86.7%) patients who demonstrated a response (ORR) to avapritinib

maintained this response as of the data cut-off. Median DOR has not been reached at the time of the latest data cut-off with a median of 26 months of follow-up in PATHFINDER and a median of 45 months of follow-up in EXPLORER.[73,76]

Patients with all disease subtypes of AdvSM demonstrated high levels of response to treatment, with ORR of 77% (95% CI 46, 95) in the ASM subgroup, 67% (95% CI 38, 88) in the MCL subgroup and 76% (95% CI 62, 86) in the SM-AHN subgroup observed in patients receiving a starting dose of 200 mg OD in PATHFINDER.[72] Although associated with uncertainty due to small patient numbers in each group, these results indicate that the magnitude of treatment effect is similar in the three groups. The demonstration of consistent efficacy across AdvSM subtypes is crucial as the accurate characterisation of the individual AdvSM subtype in any individual patient is extremely challenging and resource intensive. With efficacy shown in even the rare MCL subtype with the poorest prognosis of any disease subtype of AdvSM, patients are not at risk of futile treatment in the event of mis-categorisation of their diagnosis.

Responses were observed irrespective of prior therapy. More than half (63%) of patients in the PATHFINDER RAC-RE population had already received at least one systemic treatment, however in clinical practice the majority of patients are expected to receive avapritinib as a 1L treatment. In patients not receiving any prior systemic therapy, ORR was 90.0% (95% CI: 73.5, 97.9) compared to 64.7% (95% CI: 50.1, 77.6) in previously treated patients.[72] Similar results were observed in EXPLORER, where ORR (95% CI) was achieved in 82% (60, 95) of treatment-naïve patients and 74% (57, 88) of previously treated patients.[76]

When compared to the only other therapy indicated for use in patients with AdvSM, midostaurin,[60] the likelihood of demonstrating a response (ORR and CR) to treatment is significantly higher with avapritinib.[52] A treatment that improves remission rates and offers an opportunity of CR may increase eligibility for allo-HSCT and potential cure in AdvSM.

Strengthening the demonstration of efficacy, among all patients with AdvSM in PATHFINDER, 24-month survival was 79.0% (95% CI: 70.8, 87.3), with survival by AdvSM subtype reflecting the overall response observations. Median OS had not been reached as of the September 2022 data cut-off. In addition, significant advantages for avapritinib regarding OS have been demonstrated when compared to midostaurin.[52,53] In the ECS analysis updated with 2022 survival data from the PATHFINDER trial, patients receiving 1L avapritinib (in the label dose of 200 mg) experienced significantly improved survival compared to patients receiving 1L midostaurin (HR [95% CI]: 0.13 [0.04, 0.42]; p<0.001 and [redacted], in the RAC-RE and safety populations, respectively).[53,106] Results of the MAIC analysis also demonstrated that avapritinib produced higher likelihoods of survival compared to midostaurin.[52]

Advice from clinical experts in England is that cladribine is only used in a small proportion of patients with AdvSM and is reserved for 2L+ treatment unless rapid debulking is required. In the ECS comparative analysis, in previously treated patients, improved survival was also observed for patients treated with avapritinib compared to cladribine, although statistical significance was not reached for the updated analysis.[108] When comparing 2L+ avapritinib to

the larger cohort of patients that received 2L+ BAT, that includes midostaurin and cladribine, statistically significant improvements in OS were demonstrated when comparing 2L+ avapritinib (PATHFINDER 2022 data cut-off) to 2L+ BAT (HR [95% CI]: [redacted] and [redacted], RAC-RE and safety populations, respectively.[107] In addition, patients remained on avapritinib treatment longer than midostaurin, cladribine or BAT. In the updated analysis comparing PATHFINDER to external controls, 1L avapritinib was associated with significantly longer DOT than 1L midostaurin (HR [95% CI]: 0.26 [0.13, 0.53]; $p<0.001$) and [redacted], RAC-RE and safety populations respectively).[106] Avapritinib as a 2L+ treatment was also associated with significantly longer DOT compared with 2L+ cladribine,[108] and 2L+ BAT.[107]

Taken together, the comparison of avapritinib vs. other therapies for AdvSM demonstrates that patients receiving avapritinib live longer, respond to treatment at a greater frequency, which is associated with clinical and pathologic improvements, and remain on treatment for longer periods of time, compared to currently available therapies including midostaurin and cladribine.[7,52]

The efficacy of avapritinib is supported by its targeted mechanism of action, which has shown the greatest potency against the active conformation of KIT D816V.[11] This specificity has yielded important reductions in objective measures of mast cells in patients with AdvSM, including reductions in bone marrow infiltration by mast cells, as well as tryptase and *KIT* D816V in the blood.[48,75]

Avapritinib has also produced significant benefits in HRQoL in patients with AdvSM,[48,75] via patient perspective-based assessments, namely the EORTC QLQ-C30, which is designed to measure the ability to perform important functions of everyday living in patients with cancer, and the AdvSM-SAF, which is a symptoms-focused questionnaire for patients with AdvSM. Notably, in the pivotal PATHFINDER trial, patients demonstrated improvements in all domains of both assessment tools.[48]

Real-world experience with avapritinib further supports the efficacy findings from clinical studies.[109] In these studies, a number of patients treated with avapritinib in clinical practice achieved CR and as a result received potentially curative allo-HSCT (see Section B.1.3.2.6.2).[74,109,122] There is consensus from clinical experts in the UK that the better the response of an AdvSM patient to disease-modifying treatment pre-allo-HSCT, the better the prognosis of the patient post-allo-HSCT.[3]

Avapritinib has a well characterised safety profile with a favourable benefit-risk profile. In the updated PATHFINDER data (200 mg OD starting dose), the most common TRAEs were thrombocytopenia (40.0%), periorbital oedema (40.0%), peripheral oedema (39.0) and anaemia (29.5%).[72] The overall safety database includes 193 patients with AdvSM, of which 126 patients received avapritinib at a starting dose of 200 mg. In patients with AdvSM, safety profiles were manageable with supportive care and/or dose modifications. No new risk has been identified in patients with AdvSM based on cumulative data.[100]

Intracranial bleeding is an important risk associated with avapritinib treatment. In patients with AdvSM, the risk of intracranial bleeding has been shown to be correlated with pre-existing severe thrombocytopenia and as such avapritinib is not recommended in patients with platelet counts <50 x 10^9/L.[9] A broad spectrum of cognitive effects that are generally reversible (with intervention) can occur in patients receiving avapritinib. Cognitive effects can generally be managed with dose interruption and/or reduction.[9]

B.2.12.2 Strengths and limitations of the evidence base

PATHFINDER was designed to confirm the response rates observed in EXPLORER in AdvSM. Based on encouraging results from EXPLORER, avapritinib was studied in both midostaurin-naïve and post-midostaurin settings to understand its safety and efficacy in each population. In an effort to balance the need to address the unmet medical need for these patients and the feasibility of completing an RCT in this rare disease population and especially in those who would be evaluable by mIWG-MRT-ECNM criteria, it was decided to conduct an open-label, uncontrolled, single-arm study in patients with AdvSM to support successful registration applications. Therefore, both EXPLORER and PATHFINDER are uncontrolled single-arm trials with associated well known limitations, e.g., risk of selection bias and potential overestimation of the effect.

Interpretation of time to event endpoints, in particular PFS and OS, is hampered in the context of a single-arm trial. Current median follow-up of patients in PATHFINDER is 26 months, and median DOR has not yet been reached. Data collection is ongoing; final data are expected in Q3 2026.

Despite these limitations, the efficacy data currently available show that clinically relevant responses including unprecedented complete remissions providing the opportunity for further curative treatment can be consistently obtained with avapritinib treatment. The results from clinical trials are expected to translate to clinically meaningful outcomes for patients in clinical practice. The studies included patients with all AdvSM subtypes, included both treatment-naïve and previously-treated patients, and are reflective of the population of patients expected to be treated in clinical practice in the UK. Almost all patients in PATHFINDER received avapritinib at the expected approved starting dose (200 mg OD).

In the absence of an RCT, comparisons with external control data have been undertaken. Limitations of these analyses are discussed in Section B.2.9.4. In the MAIC, efficacy data from the midostaurin registrational trial (D2201), in addition to a second trial (A2213), was performed. The direct comparability of the patients in these trials, as well as their management, cannot be ensured. For the Blueprint Medicines ECS (BLU-285-2405), robust statistical measures have been implemented to reduce differences in baseline characteristics of the populations being compared, however similar issues with ensuring comparability of the patient populations remain.

Despite its limitations, the ECS analyses provide comparative results that are relevant in terms of:

1) The included population, which was a real-world cohort receiving treatment at centres of excellence;
2) Included comparators and expected position of avapritinib in the treatment pathway, where it is primarily expected to replace midostaurin as a 1L treatment option;
3) Outcomes assessed.

Whilst statistically significant improvements in survival were seen when comparing 1L treatment to midostaurin, an updated analysis comparing 2L+ avapritinib and 2L+ cladribine did not reach statistical significance. This may be, in part, be due to the small numbers of patients treated with cladribine (n=23) included in the analysis. In an analysis that included all 2L+ best available therapies used in the ECS, including midostaurin and cladribine, a statistically significant improvement in OS was seen. This analysis has some limitations since it includes a mix of comparators no longer used in UK clinical practice and there were some differences in the proportions of treatments previously used (more patients in the avapritinib cohort had previously received midostaurin than those in the BAT cohort), however it provides a reasonable proxy for current therapies used to treat AdvSM following previous systemic therapy.

B.3 Cost effectiveness

B.3.1 Summary of the cost-effectiveness analysis

AdvSM is a rare disease with currently only one licensed treatment, creating substantial unmet need (see Section B.1.3.3). The economic analysis presents a robust evaluation of avapritinib against current clinical practice in England.

As part of the submission, a patient access scheme (PAS) has been submitted with a simple fixed discount of [redacted]%. Results for PAS price have been modelled in the cost-effectiveness analysis.

Model summary

- A *de novo* three state partition survival model (PartSA) was developed for the economic evaluation of avapritinib compared with midostaurin and cladribine in the UK, in accordance with the NICE reference case.[123]
- A parallel state-transition model was incorporated to allow inclusion of allo-HSCT and explored as a scenario analysis.
- The analysis was conducted from an NHS/Personal Social Services (PSS) perspective, with a lifetime horizon and with costs and outcomes discounted at 3.5% per annum.[123]
- Efficacy data for avapritinib were derived from the PATHFINDER trial (September 2022 data cut-off) and efficacy for the comparator were derived from the ECS.
- Health state utility values were estimated/derived from PATHFINDER (September 2022 data cut-off) and literature identified in a targeted literature review (TLR).

Base-case results

- Avapritinib is estimated to have a large health benefit for patients versus all three comparators, generating an additional 2.86 LYs and 2.30 QALYs versus midostaurin, 1.78 LYs and 1.34 QALYs versus BAT 2L+ (as a proxy for cladribine), and 1.29 LYs and 1.23 QALYs versus cladribine.
- Treatment with avapritinib is expected to decrease the costs of treatment versus midostaurin list price, with incremental costs of [redacted] versus midostaurin, but increase costs versus BAT 2L+ (as a proxy for cladribine) and cladribine, with incremental costs of [redacted] and [redacted] respectively.
- The health benefits and costs result in ICER values for avapritinib [redacted] midostaurin, [redacted] versus BAT 2L+ (as a proxy for cladribine), and [redacted] versus cladribine.

Sensitivity analysis

- One way sensitivity analysis (OWSA) showed similar trends in all three analyses, with the discount rates (for both costs and outcomes) and age at baseline being shown to be the most sensitive parameters to variation. Disease management and cladribine administration costs were also shown to have a small impact on the results.

Summary

- Avapritinib is expected to primarily replace midostaurin in the UK in the 1L treatment setting where it shows [redacted] health benefits and [redacted] costs.
- Avapritinib addresses an unmet need for a more potent and selective therapy targeting KIT D816V, the primary underlying driver of the disease. This advancement is reflective in improved response rates and OS compared to currently available therapies.

B.3.2 Published cost-effectiveness studies

An SLR of economic evaluations, and costs and healthcare resource use were conducted on 22 June 2023 in patients with AdvSM, with an update to the search conducted on 7 November 2023 to identify relevant published cost-effectiveness studies. See Appendix G for full details of the process and methods used to select the cost-effectiveness studies relevant to the technology being evaluated. In total, one economic evaluation in AdvSM was identified in the SLR (Table 26). The study by Cariou et al., 2018 presented valid outcomes in the form of quality-adjusted life years (QALYs) and life years (LYs) in the patient population relevant to this appraisal but did not model costs.[124]

Considering the restricted applicability of the identified published economic evaluation to decision making in England, a *de novo* cost-effectiveness model was developed for the purpose of this assessment.

A summary of the published cost-effectiveness study can be found in Table 26. See Appendix G for full details of the process and methods used to select the cost-effectiveness studies relevant to the technology being evaluated.

Table 26. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Cariou et al.	2018	Partitioned survival model with a lifetime horizon, included four health states	Patients with AdvSM	Midostaurin treated patients showed quality survival gains, with an incremental gain of 1.90 QALYs versus SoC	NR	NR

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; AdvSM, advanced systemic mastocytosis; SoC, standard of care; NR, not recorded.

B.3.3 Economic analysis

The objective of the economic analysis was to assess the cost effectiveness of avapritinib compared to current clinical management in England for patients with AdvSM.

The cost-effectiveness analysis for avapritinib adopted a PartSA to reflect the natural history of patients with AdvSM; a similar approach was taken in the NICE midostaurin appraisal.[42] Aligning with NICE committee preferences and the wider precedent of utilising PartSA in oncology evaluations, the *de novo* model adopts a standard three state form PartSA approach, which was deemed appropriate for decision making in AdvSM. The analysis was conducted from the perspective of the NHS and PSS and included direct medical costs only over a lifetime horizon.

B.3.3.1 Patient population

The patient population in the economic model reflects the patient population in the pivotal trial for avapritinib, PATHFINDER.[102,114] The baseline characteristics of the patients in the PATHFINDER trial have been described in Section B.2.3.2.

This is in line with the population defined in the NICE final scope and in line with the anticipated MHRA licensed indication for avapritinib, that is, for the treatment of [redacted].

The core cost-effectiveness analysis (CEA) considers AdvSM patients from PATHFINDER clinical trial initiated on the 200 mg OD as the base-case population of the analysis. [102,114] This analysis incorporates the latest available data cut-off from September 2022, outcomes include OS, PFS, AEs, DOR and HRQoL aligned with the NICE scope.[102,114]

The viability of comparative subgroup analyses by disease subtype (ASM, SM-AHN and MCL) was considered by Blueprint Medicines. Analyses comparing the three AdvSM subtypes would be limited to naïve comparisons due to the baseline characteristics for each subtype not being reported in the comparator evidence and small patient numbers. In EXPLORER and PATHFINDER, patient numbers in the ASM and MCL subgroups treated with avapritinib in 1L therapy does not reach the minimum requirement (n=15) to perform statistically meaningful analysis. Although subgroup analyses were not performed treatment with avapritinib in the PATHFINDER study, results demonstrated high response rate with deep and durable responses regardless of disease subtype, indicating that the magnitude of treatment effect is similar in the three groups (see Section B.2.12.1).[73]

B.3.3.2 Model structure

A *de novo* PartSA was developed in Microsoft Excel® to accurately reflect the natural progression and clinical pathway of AdvSM in the UK.

B.3.3.2.1 Justification of model structure

Conducting an economic evaluation for a rare disease like AdvSM presents a significant challenge due to the scarcity of available evidence and small patient numbers in existing studies.

Oncology models usually adopt one of two approaches, cohort simulation and PartSA. The current analysis adopts a PartSA approach because it is appropriate for capturing progressive, chronic conditions with clinical outcomes requiring ongoing time-dependent risk, such as disease progression and death. Curves are directly fitted to trial outcomes, focusing on health state occupancy rather than transitions between states.

The model structure incorporated the preferences of the NICE committee from the previous midostaurin appraisal (NICE TA728), which involved consolidating the progression-free (PF) health state into one health state with a single utility value.[42]

Haematology consultants stated eligibility for and subsequent efficacy of allo-HSCT is enhanced in patients that demonstrate remission in their condition after receiving therapy (see Section B.1.3.2.6.2).

To explore those patients eligible for allo-HSCT a parallel state-transition model was included. Although the model has the flexibility to investigate allo-HSCT, allo-HSCT is not considered in the base case and instead explored in a scenario analysis (see Section B.3.3.2.3).

The PartSA approach was selected for the base-case economic evaluation as the most appropriate model structure to reflect both quality and quantity of evidence available for avapritinib and current clinical management in AdvSM.

As PATHFINDER is a single-arm trial, there is no direct head-to-head evidence comparing avapritinib versus current clinical management for AdvSM in the UK. PATHFINDER is the pivotal study demonstrating the efficacy of at the label dose of 200 mg OD as the starting dose. Therefore, OS and PFS curves from PATHFINDER were chosen as the basis of the parametric OS and PFS curves utilised in PartSA. In the absence of direct comparative evidence, key evidence for clinical outcomes (OS) is derived from the ECS IPTW analysis using data from PATHFINDER and a historical control cohort (see Sections B.2.9.2 and B.3.4).

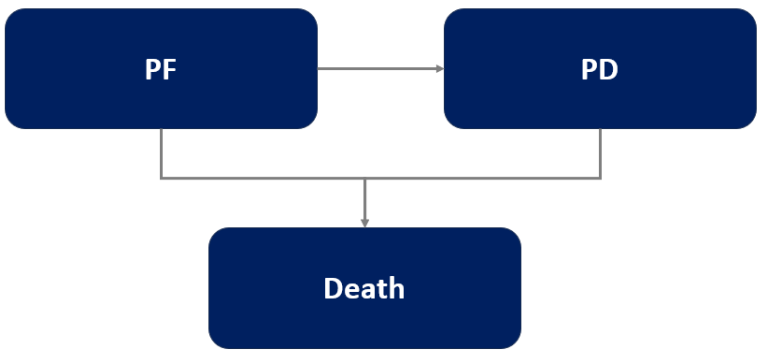
B.3.3.2.2 Model description

The PartSA is used to simulate the time in state of the cohort receiving ongoing therapy with avapritinib and UK current clinical management. The PartSA modelling technique does not allow for inclusion of additional health states that cannot be represented through mutually exclusive survival curves. Considering the lack of CR observed in midostaurin studies,[69] the rate of CR/CRh observed with avapritinib is unprecedented and provides the opportunity for further curative treatment with allo-HSCT. Therefore, to enable the inclusion of allo-HSCT as an option for a proportion of patients with CR following therapy, a state-transition model was included alongside the PartSA and explored in a scenario (see Section B.3.3.2.3).

The current base-case model includes three mutually exclusive health states: PF, PD and death (see Figure 26).

PF can be defined as stable disease, whereas progression implies a worsening of the disease. In PATHFINDER disease progression is measured using the mIWG-MRT-ECN criteria and as such only available for the RAC-RE population. Progression may occur when during the course of the disease the proliferation acquires more aggressive features, as seen in cases of AdvSM.[125] Another event typically associated with disease progression is the development of AML or the progression of the AHN.[126]

Figure 26. Model structure (PartSA base case)



Abbreviations: PartSA, partitioned survival analysis; PF, progression-free; PD, progressive disease

In the PartSA approach, state membership is determined from a set of non-mutually exclusive survival curves. The cohort enters the model in the PF health state and any transition to the PD and death health states, along the sequence, is defined by the PFS and OS curves.

The PFS curve directly provides the proportion of the cohort remaining in the PF health state over time. State membership for the death state is defined by the OS curve at each time point. For the PD health state, state membership is derived as the difference between the OS and the PFS curve at each time point, as this provides the proportion of patients who are alive but not progression-free.

The PFS and OS curves were extrapolated beyond available data from the studies to meet the requirement to model a lifetime horizon. The area under the PFS and OS curve therefore provides an estimate of mean time progression-free and life expectancy, respectively. The proportion of alive patients is "partitioned" between the PF and PD health states to allow differentiation in HRQoL and cost. This implies that in the model there is no explicit structural link between mortality and earlier progression events, and this is a known limitation of PartSA models. To ensure robustness and clinical plausibility, the extrapolation of OS was validated by UK consultant haematologists (see Section B.3.4.2).

The DOT sourced from real-world evidence (RWE) and the ECS were used to define the proportion of the cohort on treatment over time in the avapritinib and current clinical management arms.[106-109] For costing purposes, the PF and PD health states were subdivided into 'on treatment' and 'off treatment'. For both intervention and comparator, in the base-case analysis, treatment discontinuation is defined by DOT or PFS curves, whichever occurs first.

A summary of the membership and key definition of the three health states and associated sub-states in the PartSA model is presented in Table 27.

Table 27. Summary description of health states and associated sub-states in PartSA model. (base-case health states)

Health state	Sub-state	Definition	Membership
PF		Alive and stable disease (PF)	PFS
	On primary Tx	Alive, stable disease and exposed to primary tx	Minimum data point (DOT, PFS)
	Off primary Tx	Alive, stable disease and switched to post-discontinuation	PFS-PF on primary tx
PD		Alive and experienced worsening of the disease (post-progression)	OS-PFS

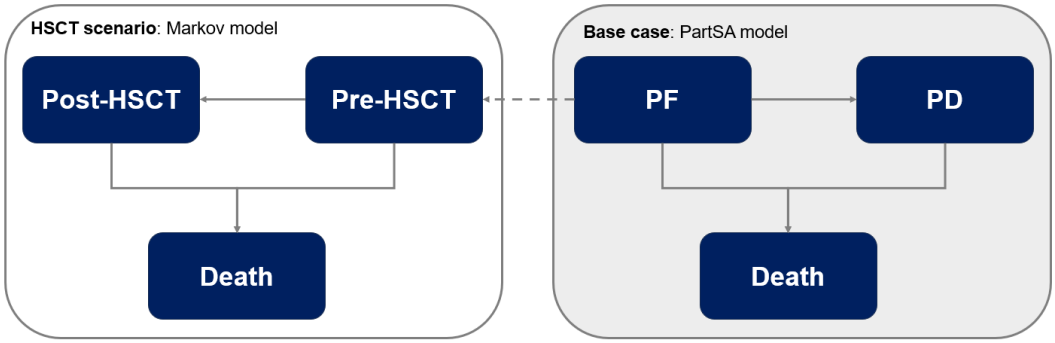
	On primary Tx	Alive, experience worsening of the disease and continue primary tx	DOT-PF on primary tx
	Off primary Tx	Alive, experienced worsening of the disease and is on post-progression treatment.	PD-PD on primary tx
Death		Dead	Total cohort-OS

Abbreviations: PD, progressive disease; PF, progression-free; N/A, not applicable; OS, overall survival; DOT, duration on treatment; Tx, treatment

B.3.3.2.3 Allogenic haematopoietic stem cell transplantation

Allo-HSCT is considered the only potential curative option for patients with AdvSM and is considered as a treatment option for a proportion of the cohort achieving CR to treatment. The model structure allows for the inclusion of allo-HSCT via a parallel health state, however allo-HSCT is excluded from the base case and explored in a scenario analysis (Figure 27).

Figure 27. Allo-HSCT scenario model structure



Abbreviations: Allo-HSCT, allogenic haematopoietic stem cell transplantation; PF, progression-free; PD, progressive disease

The health states associated with allo-HSCT are pre-allo-HSCT, post-allo-HSCT and death.

The demonstrated efficacy of avapritinib suggests that, when associated with allo-HSCT, it provides a potentially curative option for patients with AdvSM (see Section B.1.3.2.6.2).[109] However, according to clinical expert feedback the rate of increased allo-HSCT eligibility and the data regarding outcomes following treatment with avapritinib and subsequent HSCT are subject to uncertainty. Therefore, a conservative approach was taken to exclude allo-HSCT from the base case and is presented as a more optimistic scenario. Parameter inputs related to allo-HSCT can be found in Appendix N.

B.3.3.3 Features of the economic analysis

The economic analysis was conducted in accordance with the NICE reference case, implementing a lifetime horizon.[123] As per NICE guidance, the time horizon in an economic

evaluation should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.[123] As avapritinib has an impact on survival of AdvSM patients and given the typical age at diagnosis with AdvSM (the mean age at baseline was 68 years in PATHFINDER), a lifetime horizon is deemed appropriate.[72,73]

A cycle length of one month was considered appropriate (assuming 365.2425 days/12 = 30.44 days per month). A half-cycle correction was not deemed necessary due to the short cycle length.

Both costs and outcomes were discounted at 3.5% annually, as per the NICE reference case.[123] The results of the cost-effectiveness analysis are reported in terms of discounted costs per QALY gained.

The economic analysis adopts the perspective of the NHS and PSS perspective in England and Wales for costs and outcomes, aligned with NICE guidance.[123]

The results of the cost-effectiveness analysis are reported in terms of discounted costs per QALY gained. The key features of the economic analysis are described in Table 28 with a previous appraisal TA728 conducted by NICE in the same disease area, for AdvSM.[42]

Table 28. Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA728	**Chosen values**	**Justification**
Time horizon	Lifetime (until 99.99% of patients have died)	Lifetime	• A lifetime time horizon captures differential outcomes over the lifetime of the individual. • In line with the NICE reference case.[123] • Sufficient to capture all meaningful differences in technologies being compared.
Discount rate	3.5% discounting per annum applied for both costs and benefits.	3.5% discounting per annum applied for both costs and benefits.	• In line with NICE reference case.[123]
Cycle length	4 weeks	1 month (30.44 days)	• Based on the treatment cycle duration for avapritinib and short enough to capture any different in clinical outcomes between treatments.
Duration of treatment benefit	• OS, PFS and DOR for midostaurin were estimated from parametric functions fitted to the Kaplan-Meier curve for these outcomes in the D2201 trial. • OS for the comparators was estimated using the HR from a pooled analysis of D2201 and A2213 versus historical control data and applies over the lifetime horizon.	5-year treatment benefit	• DOR sourced from PATHFINDER was used in the model to capture duration of treatment benefit

	• Committee preferred a 3-year treatment benefit.		
Source of utilities	• Utilities were estimated from SF-12 data from the D2201 trial, mapped onto the EQ-5D-3L. • Decrements in utility associated with subcutaneous and injection administrations versus oral treatments were also included in the economic model.[127-129] • Utility values were adjusted for decrease in the HRQoL associated with older age.[130]	• Utilities for progression-free disease were estimated from QLQ-C30 from the PATHFINDER trial and mapped onto the EQ-5D-3L.[102] • Literature found in a TLR was used to inform quality of life of patients in progressed disease state:[131-134]: 1. Joshi et al., 2019 2. Stein et al., 2018 3. Leunis et al., 2014 4. Mamola et al., 2019 • Decrements associated in AEs were also included in the model. • Decrements in utility associated with IV treatment were also included in the economic model. • Utility values were adjusted for decrease in HRQoL associated with older age.[135]	• Utility values based on the EQ-5D-3L were included in line with the NICE reference case.[123] • As a conservative approach, the same utilities were used for avapritinib and comparators due to the absence of evidence.
Source of costs	• NHS reference costs 2017/2018 were used for resource costs.	• NHS reference costs 2021/22 were used for resource costs.[136]	• In line with the NICE reference case.[123]

	• Drug costs were derived from the BNF, eMIT and published costs where appropriate. • An existing confidential PAS is included for midostaurin.	• Drugs were derived from the BNF, eMIT and published costs where appropriate. • A confidential PAS is included for avapritinib.	
Perspective	• NHS and PSS in England and Wales.	• NHS and PSS in England and Wales.	• The perspective of costs and outcomes is that of NHS and PSS in England. • In line with NICE reference case.[123]

Abbreviations: OS, overall survival; PFS, progression-free survival; NHS, National Health Service; PSS, Personal social service; PAS, Patient access scheme; BNF; British National Formulary; eMIT, electronic market information tool; HRQoL, health-related quality of life; EQ-5D-3L, European Quality of Life 3 dimensions 3 level version; HR, hazard ratio; SF-12, 12-item Short Form Health Survey; QLQ-C30, EPRTC Core Quality of Life questionnaire.

B.3.3.4 Intervention technology and comparators

Treatments in the model include avapritinib compared with midostaurin and cladribine, in line with the NICE scope. Interferon alpha and imatinib were excluded as comparators since they are off-label therapies that are rarely used in UK clinical practice for the treatment of AdvSM and have limited evidence to support use in this indication (see Section B.1.3.1). Haematology consultants in the UK stated that:

- imatinib is only used in a small proportion of AdvSM patients, those who do not have the *KIT* D816V variant,[5,15,63]
- pegylated interferon may be used to treat AdvSM but its use in the UK is minimal.[2]

This shift in perspective aligns with the significant evolution in the NHS treatment landscape since NICE recommended midostaurin for AdvSM in 2021.[2,42]

B.3.3.4.1 Intervention

The intervention of interest in the economic analysis is avapritinib. Avapritinib is a highly potent and selective kinase inhibitor, developed to specifically target the active conformation of KIT, conferring potent and selective inhibition of KIT D816V and other activation loop mutants.[11]

The recommended expected UK license starting dosage of avapritinib is 200 mg orally, once daily in patients with AdvSM.[9] This is aligned with the regimen used in the key clinical trial supporting the submission (PATHFINDER).[9,102] Since 2 patients in PATHFINDER received a starting dose of 100 mg, these patients have been excluded from the analysis used in the economic model (as presented in Section B.2.6.1). Treatment with avapritinib is not recommended in patients with a platelet count of less than 50 x 10^9/L.[9]

As per the draft SmPC patients should "[redacted]". In accordance with this guidance, participants in the PATHFINDER trial discontinued treatment based on the trial protocol, either due to disease progression or intolerability.[9,97,102] Haematology consultants in the UK with experience prescribing avapritinib in the UK confirmed prescribing practice is in line with draft SmPC.[9]

As a result, the economic analysis does not incorporate a stopping rule for avapritinib. Instead, the model follows the treatment protocol outlined in PATHFINDER and modelled as per the expected use of avapritinib in clinical practice in the UK.

B.3.3.4.2 Comparators (defined as current clinical management in the UK)

As described in Section B.1.3.2, midostaurin is the only therapy licensed for the treatment of AdvSM in the UK and recommended by NICE.[42] Table 29 summarises the comparators

included in the economic analysis. A comprehensive summary of the treatment pathway adopted in AdvSM in the UK is illustrated in Figure 5.

Table 29. Comparators included in the economic analysis.

Comparators included in NICE scope	Comparators included in economic analysis?	Population setting	Data source	Additional notes	Justification
Midostaurin	Yes	1L	• 1L: avapritinib compared to midostaurin, using data from PATHFINDER (Sept 2022) and ECS	-	See Section B.1.3.1
Cladribine	Yes	2L+	• 2L+: avapritinib compared to cladribine, using data from PATHFINDER (Sept 2022) and ECS** • 2L+: avapritinib compared to BAT, using data from PATHFINDER (Sept 2022) and ECS*	• BAT basket comprises of a mixture of therapies, including midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%).[121] • In the base case, distribution of therapies such as midostaurin, interferons, imatinib and AML like medicines are set to 0%: • Costs associated with these therapies are excluded from the analysis. • The clinical efficacy remains the same, despite the distribution of therapies being set to 0%. Consequently, the clinical efficacy for cladribine is likely to be overestimated, given that midostaurin constitutes [redacted] of BAT basket.	See Section B.1.3.1
Imatinib	No	N/A	N/A	-	

Interferons	No	N/A	N/A		UK consultant haematologists noted that these therapies are rarely used in UK clinical practice due to the limited evidence available.[2] (see Section B.1.3.1)

Abbreviations: BAT, best available therapy; ECS, external control study; 1L, first-line setting; 2L+, second line plus setting; N/A, not applicable
*Exploratory analysis, proxy for cladribine – Haematology consultants in the UK validated BAT can be used as a proxy for cladribine as this is the only evidence available.
**The analysis involving cladribine has small patient numbers (n=27) and high levels of uncertainty (overall survival HR: [redacted]) non-significant). Therefore, the comparison involving BAT is used for illustration purposes only and is as a proxy for cladribine.

B.3.4 Clinical parameters and variables

Key efficacy data for avapritinib comes from the PATHFINDER trial where individual patient-level data (IPD) from the September 2022 data cut-off were used to inform the base-case economic analysis (see Section B.3.4.2).

Efficacy data for the comparators (current clinical management) comes from indirect evidence from PATHFINDER against a historical cohort, the external control study (see Section B.2.9).[106-108]

The sources for the clinical parameters used in the economic model are summarised below in Table 30.

From here on, comparisons versus midostaurin 1L, BAT 2L+ (as a proxy for cladribine) and cladribine 2L+ will be referred to as comparison A, B and C, respectively.

Table 30: Summary of sources of data used in economic model base case

Clinical parameter	1L vs midostaurin (comparison A)	2L+ vs BAT (proxy for cladribine, comparison B)	2L+ vs cladribine (comparison C)	Reference in submission
Baseline characteristics	PATHFINDER (September 2022) Safety 1L, 200 mg dose	PATHFINDER (September 2022) Safety 2L+, 200 mg dose	PATHFINDER (September 2022) Safety 2L+, 200 mg dose	See Section B.3.4.1
OS	ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)	ECS analysis: 2L+ avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 2L+ BAT, (IPTW sample)	ECS analysis: 2L+ avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 2L+ cladribine, (IPTW sample)	See Section B.3.4.2
PFS - avapritinib	PATHFINDER (September 2022) RAC-RE 1L, 200 mg dose	PATHFINDER (September 2022) RAC-RE 2L+, 200 mg dose	PATHFINDER (September 2022) RAC-RE 2L+, 200 mg dose	See Section B.3.4.2.1.3
PFS - comparator	ECS analysis: 1L midostaurin unweighted analysis (equivalent to comparator DOT)	ECS analysis: 2L+ BAT unweighted analysis (equivalent to comparator DOT)	ECS analysis: 2L+ cladribine unweighted analysis (equivalent to comparator DOT)	See Section B.3.4.2.2.3
DOT - avapritinib	RWE, Saunders et al 2022[109]	RWE, Saunders et al 2022[109]	RWE, Saunders et al 2022[109]	See Section B.3.4.2.2.2
DOT - comparator	ECS analysis: 1L midostaurin unweighted analysis	ECS analysis: 2L+ BAT unweighted analysis	ECS analysis: 2L+ cladribine unweighted analysis	See Section B.3.4.2.2.2
AEs - avapritinib	PATHFINDER (September 2022) RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported in >2% of patients by preferred term (safety population)	PATHFINDER (September 2022) RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported in >2% of patients by preferred term (safety population)	PATHFINDER (September 2022) RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported in >2% of patients by preferred term (safety population)	See Section B.3.4.4
AEs - comparator	Midostaurin SmPC[60]	Barete et al[127]	Barete et al[127]	See Section B.3.4.4

Abbreviations: OS, overall survival; PFS, progression-free survival; DOT, duration of treatment; AEs, adverse events; RAC-RE, Response Assessment Committee Response Evaluable population; IPTW, inverse probability of treatment weighting; BAT, best available treatment; clad, cladribine; mido, midostaurin; 1L, first line; 2L+, second line plus; RWE, real-world evidence.

An ITC was conducted to compare clinical outcomes between avapritinib-treated patients in EXPLORER and PATHFINDER and real-world patients treated with midostaurin, cladribine or BAT. The ITC was updated using data from PATHFINDER 200mg starting dose as of the September 2022 cut-off. Data from EXPLORER were not included in the updated analysis since only 20 patients received avapritinib at the expected UK licensed dose in this study, and sufficient data were available from the pivotal PATHFINDER study at this cut-off (see Section B.2.9).

The ITC used in the economic modelling consists of the following analyses:

- Patients who did not receive prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE populations of PATHFINDER compared to 1L patients receiving midostaurin in the real-world cohort.
- Patients who received prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE population of PATHFINDER compared to all patients who received cladribine as second line or later (2L+) therapy in the real-world cohort.
- Patients who received prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE population of PATHFINDER compared to all patients who received BAT as second line or later (2L+) therapy in the real-world cohort.

For each outcome of interest, where a comparison was deemed feasible (OS, DOT) for the groups of interest (listed above), an IPTW sample was generated in each case for intervention and comparator. The availability of Kaplan-Meier estimates from the adjusted set for OS (see Section B.2.9.2), informed the parameterisation of OS function in the avapritinib and comparator arms, using an independent fitting model. Treatment effect models can be found in Appendix O.

The validity of the proportional hazard's assumption was assessed using log cumulative hazards and Schoenfeld residuals plots, and the proportional hazards were assessed to be appropriate (see Appendix O). IPTW outcomes for avapritinib DOT were deemed inappropriate for informing the base case, as per feedback received from a haematology consultant in the UK. Instead, RWE was used to inform avapritinib DOT and ECS unweighted analysis were used to inform the comparators DOT (see Section B.3.4.2.1.2).

The ITC could not provide Kaplan-Meier estimates from the adjusted sets for PFS, nor an estimate for relative PFS, because the progression criteria used in the retrospective study (using real world data from different centres) were not consistent with those used in PATHFINDER (see Section B.2.9.2.2).

Therefore, outcomes assessed for real-world patients receiving BAT (including those in the groups specific to midostaurin and cladribine) were limited to the outcomes which could be most closely matched to those assessed for patients in the PATHFINDER trial, such as OS and DOT.

To address this data gap, two approaches were considered to generate PFS survival curves for the comparators: either assuming that disease progression coincides with DOT (used in

the base case) or assuming that the HR for OS holds true for PFS (see Section B.3.4.2.2.3 for more detail).

B.3.4.1 Baseline characteristics

The baseline characteristics for the modelled cohort in terms of age, gender distribution and weight were derived from PATHFINDER safety population since the patients in the trial were deemed representative of patients in UK clinical practice (Table 31).[102,114].

Table 31 features key patient characteristics as used in the model. The distribution of AdvSM patients by disease subtype (ASM, SM-AHN, MCL) and baseline characteristics have been validated as being reflective of those patients being treated in the UK by two haematology consultants. The safety population is used in the base case.[38]

The CEA includes a scenario analysis based on patients from the RAC-RE set (i.e., group of patients with evaluable response to therapy) of the PATHFINDER clinical trial on 200 mg. RAC-RE data set includes patients who fulfilled specific criteria in terms of baseline characteristics and number of completed visits (see Section B.2.4.1). However, PFS and DOR can only be determined and utilised for this population, as response was assessable solely within this subset.

Table 31. Baseline model cohort characteristics in the base case (PATHFINDER safety population)

Parameter	Baseline characteristics	
	1L patients*	2L+ patients**
No. of patients	38	67
No. of patients with ASM	7 (18.4%)	14 (20.9%)
No. of patients with SM-AHN	28 (73.7%)	41 (61.2%)
No. of patients with MCL	3 (7.9%)	12 (17.9%)
Male (%)	52.6%	61.19%
Mean age (years)	68.29	66.55
Mean weight (kg)	71.94	72.01

Source: PATHFINDER clinical summary report[72]

Abbreviations: No, number; 1L, first line setting; 2L+, second line setting.

B.3.4.2 Clinical endpoints and treatment effect

B.3.4.2.1 Avapritinib

Avapritinib time-to-event data from PATHFINDER (September 2022 data cut-off)[6] was used to estimate the OS and PFS extrapolation curves in the intervention arm, which allows the model to determine health-state membership.

The IPTW outcomes for OS in the safety population are presented further in this section. IPTW outcomes were chosen to inform avapritinib OS to allow for the use of the adjusted sets (holding increased comparability between the avapritinib and comparator sets) in both arms of the comparison. The IPTW adjusted KM curves can be found in Section B.2.9.2.4 and the IPTW outcomes RAC-RE population for OS can be found in Appendix O.

The validity of the proportional hazard's assumption was assessed using log cumulative hazards and Schoenfeld residuals plots, and the proportional hazards were assessed to be appropriate (see Appendix O).

For PFS, the model relies on the PFS curve-based estimates on the 1L and 2L+ RAC-RE analysis sets for avapritinib, given that evaluation of response to therapy was only possible in this population (see Section B.2.9.2.2): The PFS KM curve was generated considering the progression events, and the dates of progression corresponded with those reported by central-adjudicated response, by means of the mIWG-MRT-ECNM criteria.

Since the time horizon deemed appropriate for this analysis is 'lifetime', estimating the benefits associated with avapritinib over the lifetime horizon requires the extrapolation of the OS, PFS and DOT curves.

Parametric fitting of KM curves, using independent fitting model was performed to extrapolate beyond the trial observation period (September 2022 data cut-off), using the following distributions: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, Generalised Gamma, and Gamma.

The base-case analysis uses a full parametric approach, applying parametric curves from time zero to avoid abrupt shifts in the hazard as observed with KM curves. In line with the NICE Decision Support Unit (DSU) guideline on flexible methods for survival analysis, a scenario is explored following a 'piecewise approach', whereby health states membership is defined by the KM data points until available while applying the parametric curve thereafter.[137]

In the independent fitting approach, the parametric models were fitted to each treatment arm independently and was selected for the base case as they showed superior visual fit. Treatment effect models were also explored as a scenario and presented in Appendix O.

Visual inspection was carried out by plotting the projected survival curves overlaid with the KM survival functions. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used as statistical goodness-of-fit measures. Lower AIC and BIC figures are indicative of a better statistical fit for a survival function of the KM data.

Whilst statistical goodness-of-fit only provides an indication of the fit to the observed trial data, assessment of plausibility of long-term extrapolation for OS and PFS was informed by two haematology consultants. The top three best fitting curves were presented to two UK haematologist consultants who then assessed their clinical plausibility.[38] The following sub-sections outlines the treatment effect curves used in the base case for avapritinib.

B.3.4.2.1.1 Overall survival

Comparison A: Avapritinib: 200 mg OD, All AdvSM safety population, 1L setting, September 2022 data cut-off, PATHFINDER.

Table 32 features the goodness-of-fit measures for OS. For avapritinib OS (200 mg OD, 1L, safety population), AIC and BIC criteria suggest that, under the separate fitting approach, the Generalised Gamma is the best fitting distribution for OS, followed by the Exponential and the Gompertz functions (see all fitted models for OS in Figure 28).

Haematologist consultant opinion was sought to identify the most appropriate parametric function to use in the base case, with clinical experts agreeing generalised gamma was a plausible estimation for OS, in line with their own clinical experience with 1L avapritinib and therefore used in the base case.[38]

Table 32. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib OS KM (PATHFINDER, safety population, 200 mg avapritinib starting dose, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept							
ln Scale							
ln (1/Scale)							
Scale							
Shape							
AIC + BIC							
AIC							
BIC							
Ranking							

Abbreviations: OS; overall survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Figure 28. Avapritinib 200 mg OS KM curve and parametric distribution fitted (PATHFINDER, safety population, 200 mg avapritinib starting dose, 1L)

Abbreviations:1L,1st line setting; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months.
Note: The Exponential and the Gama distributions in the chart run very close together, visually showing the gamma and the Exponential curve under the same curve (in purple)
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Comparison B: Avapritinib: 200 mg OD, All AdvSM safety population, 2L+, versus BAT (as a proxy for cladribine), September 2022 data cut-off, PATHFINDER

Table 33 features the goodness-of-fit measures for OS. For avapritinib OS (200 mg OD, 2L+, all AdvSM safety population, versus BAT as a proxy for cladribine), AIC and BIC criteria suggests that Exponential is the best fitting distribution for OS, followed by the Log-logistic and the Gamma functions (see all fitted models for OS in Figure 29).

Haematologist consultant expert opinion was sought to identify the most appropriate parametric function to use in the base case, with clinical experts agreeing Exponential was a plausible estimation for OS, in line with their own clinical experience with 2L+ avapritinib and therefore used in the base case.[38]

Table 33. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib OS KM versus BAT as a proxy for cladribine (PATHFINDER, safety population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln (1/Scale)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS; overall survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion; 2L+, second line plus; clad, cladribine.
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Figure 29. Avapritinib 200 mg OS KM curve and parametric distribution fitted (PATHFINDER, safety population, 200 mg avapritinib starting dose, 2L+)

Abbreviations:2L+, Second line plus; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Comparison C: Avapritinib: 200 mg OD, All AdvSM safety population, 2L+, versus cladribine, September 2022 data cut-off, PATHFINDER

Table 34 features the goodness-of-fit measures for OS, AIC and BIC criteria suggests that Exponential is the best fitting distribution for OS, followed by the Log-logistic and the Gompertz functions (see all fitted models for OS in Figure 30).

UK clinical expert opinion was sought to identify the most appropriate parametric function to use in the base case, clinical experts were conflicted in opinion as Exponential and Gompertz were suggested as clinically plausible. As Exponential had the best statistical fit, it was chosen for the base case.[38]

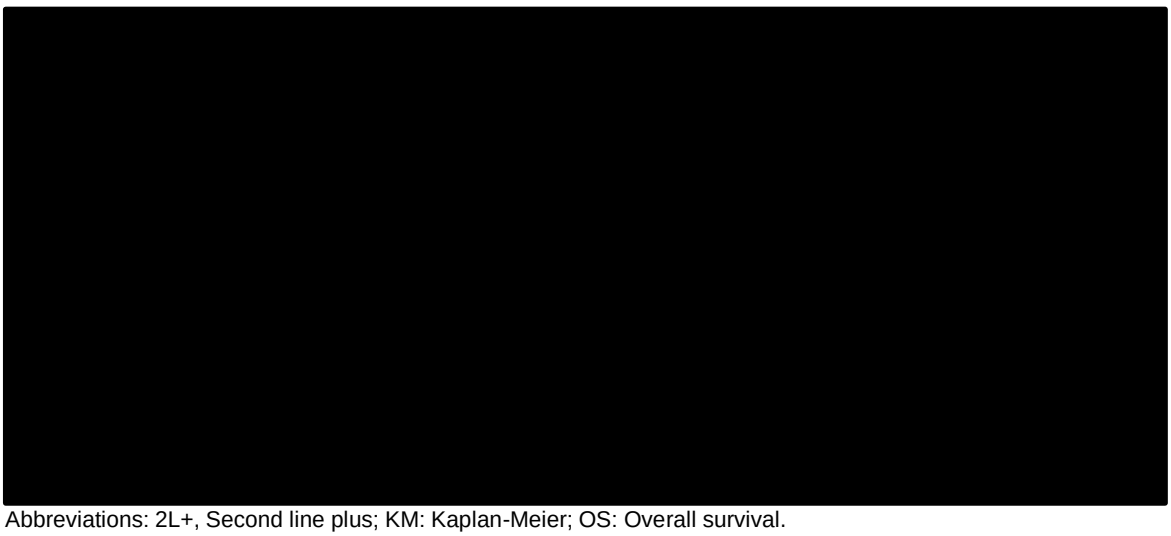
Table 34. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib OS KM versus cladribine (PATHFINDER, safety population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept							
ln Scale							
ln (1/Scale)							
Scale							
Shape							
AIC + BIC							
AIC							
BIC							
Ranking							

Abbreviations: DOT; duration of treatment; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion; clad: cladribine

Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Figure 30. Avapritinib 200 mg OS KM curve and parametric distribution fitted (PATHFINDER, safety population, 200 mg avapritinib starting dose, 2L+)



Abbreviations: 2L+, Second line plus; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

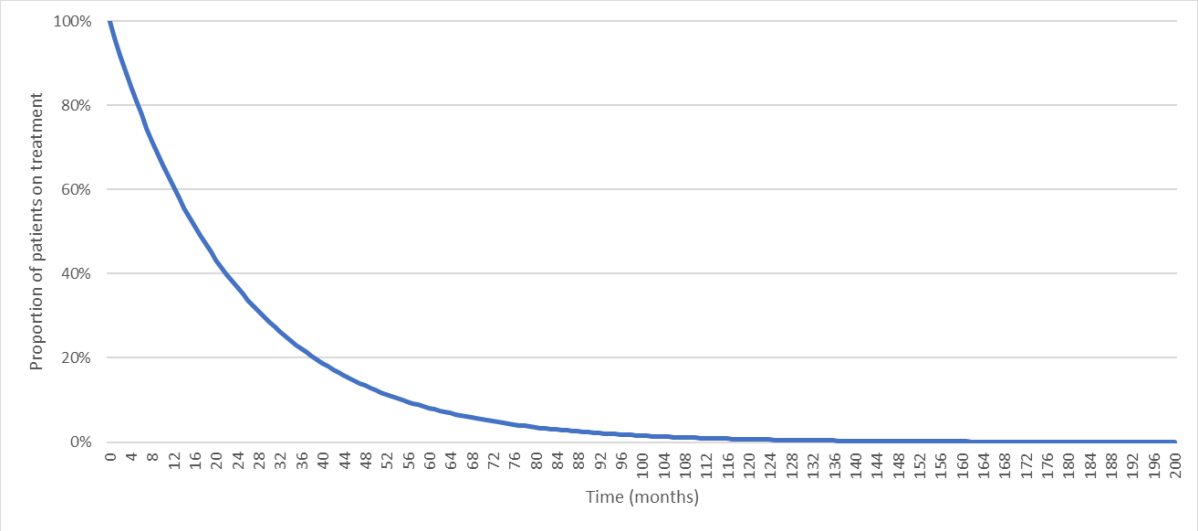
B.3.4.2.1.2 Duration of treatment

Two sources of data are available to inform DOT for avapritinib: median DOT in patients treated with avapritinib in PATHFINDER (September 2022 data cut-off) in the IPTW analysis of the ECS and RWE from patients in the UK collected by Saunders et al. where a median duration of treatment of 504 days (range 75 - 1168 days) was reported (see Section B.2.6.3).[109]

Although IPTW outcomes for DOT were available, since this data is from patients in the UK who received treatment with avapritinib in clinical practice, this was deemed to be an appropriate source to use for expected treatment duration. Additionally, the comparators in this economic analysis are subjected to a similar approach by utilising RWE from the ECS (retrospective historical cohort). Therefore, ensuring a fair and contextually relevant basis for comparison, RWE for avapritinib is used in the base case and IPTW outcomes from PATHFINDER (September data cut-off) is presented as a scenario analysis (see Appendix O for IPTW curves).

To generate the parametric curves from the RWE, exponential extrapolations were estimated using the median time on treatments (see Figure 31).

Figure 31. Avapritinib DOT parametric distribution fitted (Saunders et al.)



B.3.4.2.1.3 Progression-free survival

The process of extrapolating PFS curves for avapritinib mirrored that outlined for OS and DOT. To maintain consistency between the extrapolation of PFS and OS, the minimum value between PFS and OS was utilised.

Since comparisons between avapritinib and current clinical management were unfeasible (as outlined in Section B.3.4.2), avapritinib PFS curve was based on an unweighted sample.

Avapritinib: 200 mg OD, RAC-RE population, 1L setting, September 2022 data cut-off, PATHFINDER.

For avapritinib PFS (200 mg OD, 1L, RAC-RE population), AIC and BIC criteria suggest that Exponential is the best fitting distribution for PFS, followed by the Log-normal and the Generalised Gamma functions (see all fitted models for PFS in Figure 32). Validation from two UK haematologist consultants were sought to identify the most appropriate parametric function to use in the base case, with clinical experts agreeing Generalised Gamma was a plausible estimation for PFS, in line with their own clinical experience with 1L avapritinib.[38]

Table 35. Goodness of fit measures: Objective fitting parametric models to observed avapritinib PFS KM (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS; progression-free survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion; RAC-RE: Response Assessment Committee Response-Evaluable.
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Figure 32. Avapritinib 200 mg PFS KM curve and parametric distributions fitted (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose, 1L)

Abbreviations:1L, 1st line setting; AdvSM: advanced systemic mastocytosis; KM: Kaplan-Meier; PFS: Progression-free survival; RAC-RE: Response Assessment Committee Response-Evaluable.
Note: Time is defined in months
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Avapritinib: 200 mg OD, RAC-RE population, 2L+, September 2022 data cut-off, PATHFINDER

For avapritinib PFS (200 mg OD, 2L+, RAC-RE population), AIC and BIC criteria suggest that log-normal is the best fitting distribution for PFS, followed by the Gompertz and the log-logistic functions (see all fitted models for PFS in Figure 33).

UK clinical experts were conflicted in opinion as Log-normal and Gompertz were suggested as clinically plausible. As Log-normal had the best statistical fit, it was chosen for the base case.[38]

Table 36. Goodness of fit measures: Objective fitting parametric models to observed Avapritinib PFS KM (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS; progression-free survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion; RAC-RE: Response Assessment Committee Response-Evaluable.
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Figure 33. Avapritinib 200 mg PFS KM curve and parametric distributions fitted (PATHFINDER, RAC-RE population, 200 mg avapritinib starting dose, 2L+)

Abbreviations: 2L+, Second line plus; AdvSM: advanced systemic mastocytosis; KM: Kaplan-Meier; PFS: Progression-free survival; RAC-RE: Response Assessment Committee Response-Evaluable.
Note: Time is defined in months
Note: The data cut-off for this analysis was 9 September 2022. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

B.3.4.2.1.4 Duration of treatment benefit

Data from PATHFINDER indicate that the DOR to avapritinib may extend to 5 years or more. As of the September 2022 data cut-off, median DOR for all responders was not reached. Of patients who demonstrated an ORR to avapritinib, 86.7% maintained this response as of the data cut-off, with median follow-up >2 years. The KM estimate for the proportion of patients continuing to respond at 42 months is 70.5% (see Table 11), indicating that most patients will continue to respond for at least 3.5 years.[73]

Therefore, a 5-year treatment benefit is applied to avapritinib in the base case and a 1-year, 3-year and 10-year treatment benefit has been explored in a scenario analysis.

B.3.4.2.2 Comparators

Clinical data is derived from the ECS IPTW analysis from PATHFINDER and historical cohort. The ITC facilitated the estimation of IPTW outcomes, thereby improving the comparability of the data. This led to the derivation of weighted KM estimates enabling the parameterisation of the OS KM curves. IPD for the BAT cohort were collected retrospectively (see Section B.2.9).

The summary of data sources for comparisons between avapritinib and current clinical management is presented in Table 30.

The approach used to inform PFS in the comparator arm is explained further in this section.

As described in Section B.3.4.2, parametric fitting of the KM curves using an independent fitting approach was carried out using the same methodology outlined for the avapritinib arm.

Independent fitting model was used in the base case, as they showed a superior visual fit. Treatment effect models were explored as a scenario, with inputs available for this option presented in Appendix O.

B.3.4.2.2.1 Overall survival

Comparison A: Midostaurin, all AdvSM safety population, 1L

Table 37 feature the goodness-of-fit measures for OS. For midostaurin OS (1L, all AdvSM safety population), AIC and BIC criteria suggest that, under the separate fitting approach, Log-normal is the best fitting distribution for OS, followed by the Exponential and the log functions (see all fitted models for OS in Figure 34**).**

Two consultant haematologists in the UK agreed the Exponential curve was a plausible estimation for OS, in line with their own clinical experience with 1L midostaurin and therefore used in the base case.[38]

Table 37. Goodness of fit measures: Objective fitting parametric models to adjusted midostaurin OS KM (safety population, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, Overall survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 1L) versus 1L midostaurin (IPTW sample).

Figure 34. Midostaurin adjusted OS KM curve and parametric distributions fitted (safety population, 1L)

Abbreviations:1L, 1st line setting; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months.
Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 1L) versus 1L midostaurin (IPTW sample).

Comparison B: BAT (as a proxy for cladribine), All AdvSM safety population, 2L+

Table 38 features the goodness-of-fit measures for OS. For BAT OS (2L+, all AdvSM safety population), AIC and BIC criteria suggest that, under the independent fitting approach, Gompertz is the best fitting distribution for OS, followed by the log logistic and the Weibull functions (see all fitted models for OS in Figure 35).

UK clinical expert opinion was sought to identify the most appropriate parametric function to use in the base case, with clinical experts agreeing Weibull was a plausible estimation for OS, in line with their own clinical experience with 2L+ cladribine (BAT as a proxy).[38]

Table 38. Goodness of fit measures: Objective fitting parametric models to adjusted BAT OS KM (Safety population, 2L+ setting)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, Overall survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 2L+) versus 2L+ BAT (IPTW sample).

Figure 35. BAT adjusted OS KM curve and parametric distributions fitted — Safety population, 2L+ setting

Abbreviations:2L+, Second line or higher; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months
Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 2L+) versus 2L+ BAT (IPTW sample).

Comparison C: Cladribine, All AdvSM safety population, 2L+

Table 39 features the goodness-of-fit measures for OS. For cladribine OS (2L+, all AdvSM safety population), AIC and BIC criteria suggest that, under the separate fitting approach, Gompertz is the best fitting distribution for OS, followed by the Log-normal and the Weibull functions (see all fitted models for OS Figure 36). Following visual inspection, no issues with this choice where identified.

UK clinical expert opinion was sought to identify the most appropriate parametric function to use in the base case, with clinical experts agreeing Exponential was a plausible estimation for OS, in line with their own clinical experience with 2L+ cladribine.[38]

Table 39. Goodness of fit measures: Objective fitting parametric models to adjusted cladribine OS KM (Safety population, 2L+ setting)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, Overall survival; KM, Kaplan-Meier; OD, once daily; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 2L+) versus 2L+ cladribine (IPTW sample).

Figure 36. Cladribine OS adjusted KM curve and parametric distributions fitted — Safety population, 2L+ setting

Abbreviations:2L+, Second line or higher; KM: Kaplan-Meier; OS: Overall survival.
Note: Time is defined in months
Note: the source of this data is from the ECS analysis of PATHFINDER (200 mg avapritinib starting dose, safety population, September 2022 data cut-off, 2L+) versus 2L+ cladribine (IPTW sample).

B.3.4.2.2.2 Duration of treatment

Since RWE for DOT is used for avapritinib in the base case, median DOT from ECS is used for the comparators, reported as: [redacted] months for midostaurin (see Figure 37); [redacted] months for BAT (as a proxy for cladribine) (see Figure 38) and [redacted] months for cladribine (see Figure 39).

To ensure a fair comparison, an exponential extrapolation was applied to generate the parametric curves using the median DOT from ECS, identical to avapritinib. A scenario analysis was explored using IPTW ECS analysis comparing avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs comparator (IPTW sample).

Figure 37: Midostaurin 1L DOT parametric distribution fitted (unweighted sample ECS)

Note: Data from unweighted historic cohort from external control study

Figure 38: BAT (as a proxy for cladribine) 2L+ DOT parametric distribution fitted (unweighted sample ECS)

Note: Data from unweighted historic cohort from external control study

Figure 39: Cladribine 2L+ DOT parametric distribution fitted (unweighted sample ECS)

Note: Data from unweighted historic cohort from external control study

B.3.4.2.2.3 Progression-free survival in the comparator arm

As mentioned in Section B.2.9.2.2, PFS was not analysed in the external control study (informing the indirect treatment comparison) because disease progression in the retrospective real-world cohort was generally not recorded or not recorded in a way that was consistent with PATHFINDER, hindering comparability.

No data for PFS for current clinical management were identified, and in the absence of evidence, two approaches were considered for dealing with this limitation, allowing the estimation of PFS survival curve for the comparator arms:

- **First approach, used in the base-case analysis**: Using the comparator's DOT curve as proxy for the comparator's PFS curve (comparator PFS is assumed to be the same as comparator DOT). UK clinical expert deemed it is reasonable to assume comparator DOT as a proxy for PFS, this choice is supported by the expectation of comparator treatments being administered until progression.[38] Please note that the application of DOT had changed from the version presented to clinicians, however it is anticipated the results will show minimal difference.
- **Second approach**, **used in scenario analysis:** Comparator PFS can also be estimated by applying the OS HR (resulting from the IPTW ITC) to the parametrised avapritinib PFS curve. Such an approach relies on the assumption that the OS HR holds also for PFS, and that the proportional hazard assumption is met. Note that a potential hurdle of this approach is that the DOT curve might cross the PFS curve, in which case the comparator treatments would be assumed to continue after progression until the treatment discontinuation as defined by DOT occurs.

Figure 40, Figure 41 and Figure 42 reflect the approach used for PFS in the base-case, for midostaurin and BAT (proxy for cladribine) and cladribine respectively.

Figure 40. Midostaurin – survival curves defining health states membership (safety population, as per base case)

Note: This chart reflects only survival extrapolations, according with the distributions selected It does not reflect the impact of including allo-HSCT in the analysis (which is explored in a scenario analysis)
Abbreviations: BAT; best available therapy; TOT, time on treatment; PFS, progression-free survival; OS, overall survival

Figure 41. BAT survival curves defining health state membership (safety population)

Note: This chart reflects only survival extrapolations, according with the distributions selected in the text above. It does not reflect the impact of including Allo-HSCT in the analysis (which is explored in a scenario analysis)
Abbreviations: BAT; best available therapy; TOT, time on treatment; PFS, progression-free survival; OS, overall survival

Figure 42. Cladribine survival curves defining health state membership (safety population)

Abbreviations: TOT, time on treatment; PFS, progression-free survival; OS, overall survival

Table 40 below shows an overview of the OS HRs sourced from the ITC to inform the second approach. This approach is explored in a scenario analysis. Statistical significance was established in the updated results, as a two-sided P-value < 0.05 was considered statistically significant without multiplicity adjustment.

Table 40. Hazard ratios (adjusted HRs for the safety sets, IPTW samples)

IPTW samples	Analysis	Adjusted HR (confidence intervals)	P-values
ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)	OS	[redacted]	[redacted]
ECS analysis: 2L+ avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 2L+ cladribine, (IPTW sample)	OS	[redacted]	[redacted]
ECS analysis: 2L+ avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 2L+ BAT, (IPTW sample)	OS	[redacted]	[redacted]

Abbreviations: BAT; best available therapy; TOT, time on treatment; PFS, progression-free survival; OS, overall survival

B.3.4.3 Non-disease-specific mortality

All-cause mortality rates specific to age and sex were calculated for the general UK population in each cycle. In instances where the modelled OS indicated a lower mortality than that of the general population, the all-cause mortality hazard rate from the UK Office of National Statistics (ONS) was used instead of the study-based estimate.[138] This corrects for the long tails observed in some of the parametric fits for all interventions and comparators.

B.3.4.4 Adverse events

The incidences of AEs associated with avapritinib in the model were based on data from PATHFINDER trial (September 2022 data cut-off).[102,114] The analysis included only grade 3 and above AEs observed in at least 2% of the patients treated with an avapritinib dose of 200 mg OD, as reported in Table 30 of the clinical study report.[72] The AE incidences were then included in the model after adjusting for the monthly cycle length (Table 41).

The incidence of AEs in midostaurin was based on the data reported in the summary of product characteristics.[60] The incidence of AEs in cladribine was based on data reported by Barete et al.[127]

Table 41 reports the cycle probability of 3+ AEs used in the model.

Table 41. Cycle probabilities of grade 3+ AEs

	Avapritinib	Midostaurin	Cladribine
Thrombocytopenia	0.009727[72]	0.000000[60]	0.014337[127]
Anaemia	0.014245[72]	0.000000[60]	0.016425[127]
Other haematological disorders	0.003169[72]	0.002455[60]	0.010608[127]
Gastrointestinal bleed	0.000000[72]	0.000355[60]	0.000000[127]
Acute myeloid leukaemia	0.000000[72]	0.000213[60]	0.000000[127]
Sepsis	0.000000[72]	0.000798[60]	0.000978[127]
Heart failure or shock	0.000000[72]	0.000070[60]	0.000000[127]
Cardiac arrest	0.000000[72]	0.000000[60]	0.000000[127]
Cerebrovascular accident, nervous system infections, or encephalopathy	0.000000[72]	0.000000[60]	0.000000[127]
Haemorrhagic cerebrovascular disorders	0.000000[72]	0.000000[60]	0.000000[127]
Non-malignant gastrointestinal tract disorders	0.000564[72]	0.000467[60]	0.000000[127]
Non-malignant hepatobiliary or pancreatic disorder	0.001045[72]	0.000701[60]	0.000000[127]
Pneumonia	0.001795[72]	0.000723[60]	0.000000[127]
Pleural effusion	0.000000[72]	0.000428[60]	0.000000[127]
Low back pain	0.000000[72]	0.000000[60]	0.000000[127]
Hypertension	0.001340[72]	0.000000[60]	0.000000[127]
Syncope or collapse	0.000000[72]	0.000000[60]	0.000000[127]

	Avapritinib	Midostaurin	Cladribine
Unspecified oedema	0.001359[72]	0.000213[60]	0.000000[127]
Tendency to fall, senility or other condition affective cognitive functions	0.000000[72]	0.000000[60]	0.000000[127]
Fever of unknown origin	0.000000[72]	0.000428[60]	0.000546[127]
Breast disorders	0.000000[72]	0.000000[60]	0.000000[127]
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	0.000670[72]	0.000477[60]	0.000000[127]
Sleep disorders	0.000000[72]	0.000000[60]	0.000000[127]
Other respiratory disorders	0.001340[72]	0.000262[60]	0.000000[127]
Headache, migraine or cerebrospinal fluid leak	0.000000[72]	0.000105[60]	0.000000[127]
Peripheral vascular disorders	0.000000[72]	0.000141[60]	0.000000[127]
Kidney or urinary tract infections	0.000000[72]	0.000000[60]	0.000000[127]
Skin disorders	0.000000[72]	0.000141[60]	0.000000[127]
Weight increased	0.001795[72]	0.000000[60]	0.000000[127]
Appendicitis	0.001340[72]	0.000000[60]	0.000000[127]
Chronic kidney disease	0.001340[72]	0.000000[60]	0.000000[127]
Cognitive disorder	0.001340[72]	0.000000[60]	0.000000[127]
Renal failure	0.001340[72]	0.000000[60]	0.000000[127]
Non-malignant, ear, nose, mouth, throat or neck disorders	0.000000[72]	0.000283[60]	0.000000[127]

Abbreviations: AEs, adverse events.

B.3.5 Measurement and valuation of health effects

B.3.5.1 Health-related quality of life data from clinical trials

As described in Section B.2.6.1.5.1, HRQoL was collected in EXPLORER and PATHFINDER using EORTC QLQ-C30.[97,102,113,114] As per study protocol, assessments for

both questionnaires in PATHFINDER were scheduled to occur at baseline, at end of Week 2, Week 4 and Week 8 and subsequently, every 8 weeks until cycle 17 (i.e., at 64 weeks) and if, occurring prior to cycle 17, at end of study/treatment.

As EORTC QLQ-C30 is not a preference-based measure of HRQoL and does not adhere to the NICE reference case, EORTC QLQ-C30 was mapped to the EQ-5D-3L using a published algorithm (see Section B.3.5.2).

B.3.5.2 Mapping

EQ-5D were not available from either EXPLORER or PATHFINDER, therefore, to align with the recommendations of the NICE methods guide and produce EQ-5D data, EORTC QLQ-C30 from PATHFINDER were mapped onto the EQ-5D-3L using published algorithms derived from UK tariffs.

The NICE methods guide specifies that data obtained using an EQ-5D preference-based measure is the preferred choice for inclusion in economic evaluations, provided it is available.

A TLR was conducted to identify a suitable mapping algorithm to transform the EORTC QLQ-C30 to EQ-5D-3L utility values. The TLR identified a total of 6 papers reporting an algorithm suitable to the present analysis. To select a final algorithm among the studies identified, several key aspects of the included populations were compared with the ones of AdvSM patients. Key aspects range from baseline characteristics, like age, geographical area, type of disease and prognosis. A full description of the TLR methodology and results is reported in Appendix P.

The algorithm published by Young et al. investigated a range of potential models to develop mapping functions from two widely used cancer-specific measures (including QLQ-C30) to predict EQ-5D-3L values.[139] The analysis was based on 771 patients with multiple myeloma (N=512), breast cancer (N=100) and lung cancer (N=99). The algorithm published by Young et al. was deemed to be the best-choice for the AdvSM population and was applied to the avapritinib dataset to obtain health utility values, given that no other suitable algorithm was found during the TLR.

To map EORTC QLQ-C30 scores to EQ-5D values the utilities were stratified by progression status: First, the progression date of each patient was identified and all the QoL observations prior to that date were used to calculate the average PF utility value for each patient. Finally, the average of each patient values was aggregated in a single score.

While this approach provided reliable results for the utility value associated with the PF health state, it proved futile to define the utility value after progression, since there was only one QoL observation for patients with a PD in the datasets, even when pooling observations from EXPLORER and PATHFINDER to increase the sample size.[97,102] Therefore, a targeted literature review was conducted to inform the model.

B.3.5.3 Health-related quality of life studies

An SLR was conducted to identify relevant HRQoL data in patients with AdvSM. Searches were conducted in June and updated in November 2023, full details of the SLR strategy, study selection process and results are reported in Appendix H.

In the update review of 19 publications initially identified and screened from multiple databases, all 19 studies were excluded due to population, study design and outcomes criteria not being met, and none were identified through grey literature searching. As the SLR search yielded no relevant studies meeting the inclusion criteria, literature found in a TLR were included to fill gaps associated with the progressed health state utility. The TLR strategy is reported in detail in Appendix P.

Based on the findings of the TLR, four papers were used to calculate the ratio between progression-free and PD utility values (Table 42). Two papers were based on Time Trade-Off (TTO) and Discrete Choice (DC) experiments conducted on the general population.[131,132] The two other papers were based on utility scores measured directly on actual patients.[133,134]

To create an aggregate ratio both a plane average and a weighted average (i.e. base-case analysis) were estimated, with the number of patients in each paper defining the weights. The ratio between the two scores were then calculated and applied to the PFS utility that was based on PATHFINDER data. This approach still considers the original AdvSM population and simply uses the identified ratio to correct the utility value parameter. This minimises the bias related to the fact that proxy conditions were used instead of AdvSM. Baseline characteristics reported in the literature identified in the TLR can be found in Appendix P.

Table 42. TLR on QoL after AdvSM progression – results

Author	Country	Study design	Pathology	n. patients	PF QoL	PD QoL	Data collection methodology
Stein 2018	US	Cross-sectional	AML	300	Utility in CR: 0.87	Utility at relapse: 0.355	Discrete choice experiment in US
Joshi 2019	UK	Cross-sectional	AML	210	Utility in long-term follow-up: 0.89	Utility in R/R patients: 0.51	TTO UK population

Author	Country	Study design	Pathology	n. patients	PF QoL	PD QoL	Data collection methodology
Leunis 2014	NL	Cross-sectional	AML	92	CR after 1L, non-relapsed: 0.83	Utility in R/R patients: 0.78	Not reported
Mamolo 2019	US	Cross-sectional	AML	439	0.74	0.73	US Tariff

Abbreviations n,number; PF, progression-free; PD, progressive disease; QoL, quality of life; CR, complete response; US, United States; UK, United Kingdom; NL, Netherlands; TTO, time trade-off; AML, acute myeloid leukaemia; 1L, first line.

B.3.5.4 General population utility value

The study utilises age and gender specific utility values form the general population, as reported by Hernandez et al., to adjust the cohort's utility values for ageing.

B.3.5.5 Adverse reactions

In addition to the utilities associated with each health state, a disutility was applied at each cycle, reflecting the reduction in quality of life due to the AEs. Each disutility value was corrected for the cycle probability and the duration of the correspondent adverse event. To inform the model, both published literature and previous health technology assessment (HTA) submissions (TA627 and TA604) were used, as reported in Table 43.[140,141] Some of the adverse events were grouped under a single definition. In this case an aggregate disutility value and an aggregate AE duration were calculated through a plane average.

Table 43. Disutilities of grade 3+ AEs

	Disutility	Duration (days)	Source
Thrombocytopenia	-0.108	23.23	NICE TA627[140]
Anaemia	-0.119	16.07	NICE TA627[140]
Other haematological disorders	-0.088	24.846	NICE TA627[140] Sullivan 2011[142]
Gastrointestinal bleed	-0.0512	NR	Sullivan 2011[142] Shabaruddin 2013[143]
Acute myeloid leukaemia	-0.175	NR	Shabaruddin 2013[143]
Sepsis	-0.267	34	NICE TA627[140]
Heart failure or shock	-0.063	NR	NICE TA604[141] NICE TA627[140] Sullivan 2011[41]
Cardiac arrest	-0.063	NR	Sullivan 2011[142]
Cerebrovascular accident, nervous system infections, or encephalopathy	-0.086	NR	Sullivan 2011[142]
Haemorrhagic cerebrovascular disorders	-0.117	NR	Sullivan 2011[142]
Non-malignant gastrointestinal tract disorders	-0.050	25.11	NICE TA604[141] NICE TA627[140] Sullivan 2011[41]
Non-malignant hepatobiliary or pancreatic disorder	-0.042	NR	Sullivan 2011[142]
Pneumonia	-0.200	14	NICE TA627[140]
Pleural effusion	-0.078	NR	Sullivan 2011[142]
Low back pain	-0.144	NR	Sullivan 2011[142]
Hypertension	-0.038	NR	Sullivan 2011[142]
Syncope or collapse	NR	NR	NR
Unspecified oedema	-0.060	NR	Shabaruddin 2013[143]

	Disutility	Duration (days)	Source
Tendency to fall, senility or other condition affective cognitive functions	NR	NR	NR
Fever of unknown origin	-0.110	12.3	NICE TA604[141]
Breast disorders	-0.003	NR	Sullivan 2011[142]
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	-0.094	33.42	NICE TA604[141] NICE TA627[140]
Sleep disorders	-0.066	NR	Lubetkin 2018[144]
Other respiratory disorders	-0.041	12.72	NICE TA604[141] Sullivan 2011[142]
Headache, migraine or cerebrospinal fluid leak	-0.023	NR	Sullivan 2011[142]
Peripheral vascular disorders	-0.057	8	NICE TA627[140]
Kidney or urinary tract infections	-0.005	NR	Sullivan 2011[142]
Skin disorders	-0.195	34	NICE TA627[140]
Weight increased	0.000	NR	Assumed zero.
Appendicitis	-0.088	NR	NR assumed average of all other AEs
Chronic kidney disease	-0.088	NR	NR assumed average of all other AEs

	Disutility	Duration (days)	Source
Cognitive disorder	-0.088	NR	NR assumed average of all other AEs
Renal failure	-0.088	NR	NR assumed average of all other AEs
Non-malignant, ear, nose, mouth, throat or neck disorders	0.010	NR	Sullivan 2011[41]

Abbreviations: N/R; not recorded.

B.3.5.6 Decrement in utility associated with mode of administration.

Feedback from consultant haematologists suggest cladribine is administered sub-cutaneously.[38] Therefore, the economic model explores disutility associated with subcutaneous administration and the benefit associated with the availability of an oral treatment over existing treatments, as acknowledged in previous NICE appraisals.[42]

The methodology followed aligns with approach outlined in NICE TA728.[42] Estimated utility decrements associated with different modes of administration was explored by Matza et al., 2013. The study adopts a TTO approach involving 121 individuals' various treatments for bone cancer which were considered. A utility once a month and a utility decrement of -0.037 (SD: 0.106) in patients receiving a 2-hour injection infusion once every four weeks was reported.

In patients initiating cladribine the decrement in utility was calculated into a decrement in QALY applied at the onset of the model. This calculation was based on a utility decrement of -0.074 and doubled to reflect the greater frequency of administration (day 1-5 versus once every 4 weeks) and the anticipated treatment duration (calculated to be a median number of cycles 3.68 from Barete et al. 2015).[127,128]

B.3.5.7 Health-related quality of life data used in the cost-effectiveness analysis.

The base-case utility values for PFS health state were derived from PATHFINDER as this was considered the most robust and applicable source of utility data for this population, as data were directly collected from patients with AdvSM. The values were mapped to EQ-5D-3L which is the preferred method outlined in the NICE reference case.[123]

As stated in Section B.3.5.3, mapping algorithm requires utility to be stratified by progression status and due to the small sample sizes, this was not possible. Therefore, data from literature was considered robust to address the data gap.

Health state utility values (HSUVs) were applied consistently across treatment arms by progression status and line of therapy. When a patient moves from pre-progression to post-progression state, their utility decreases. It is also assumed patients receiving 2L+ therapy have lower utility at baseline, as they have experienced disease progression previously and therefore have lower HSUVs than 1L patients. Consultant haematologists in the UK agreed HSUVs presented for 1L and 2L+ patients were representative of those patients in the UK. Progression free values for 2L+ therapy also align with results from PRISM study.[47]

HSUVs were adjusted over the lifetime time horizon by applying age-related decrements to reflect the ageing of the cohort. Age-related utility decrements were included in the model base case to account for the natural decline in QoL associated with age.

Table 44 summarises the utility values included in the cost-effectiveness base-case. In addition to treatment specific AEs, disutility associated with cladribine administration was included, as described in Section B.3.5.6.

Table 44. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Standard error	Reference in submission (section and page number)	Justification
Progression-free (1L)	[redacted]	[redacted]	B.3.5.1	Derived from PATHFINDER and validated by UK consultant haematologists[38, 114]
Progressed disease (1L)	[redacted]	[redacted]	B.3.5.3	Validated by UK consultant haematologists[38]
Progression-free (2L+)	[redacted]	[redacted]	B.3.5.1	Derived from PATHFINDER and validated by UK consultant haematologists[38, 114]
Progressed disease (2L+)	[redacted]	[redacted]	B.3.5.3	Validated by UK consultant haematologists[38]
Death	0.000	-	-	-

Abbreviations: 1L, first line; 2L+, second line plus

B.3.6 Cost and healthcare resource use identification, measurement and valuation

An SLR was performed to identify relevant costs and resource use studies for incorporation in the model. The searches were conducted in November 2023 and comprehensive details of the SLR search strategy, study selection and results are provided in Appendix I.

In total, five studies were identified during the SLR, and all five studies were carried out in the United States and therefore limiting their applicability to clinical practice in England. As a result, no data from these studies were used in the economic analysis.

B.3.6.1 Intervention and comparators' costs and resource use

Costs included in the economic analysis were drug acquisition costs, administration costs, expenses related to AEs, expenditures for disease monitoring and end-of-life costs.

All costs were valued in 2022 UK pounds. Where necessary, costs were inflated to 2022/23 prices using the hospital and community health services (HCHS) pay and prices index from the Unit Costs of Health and Social Care, as issued by the Personal Social Services Research Unity (PSSRU).[145]

B.3.6.1.1 Drug acquisition costs of intervention and comparators

The recommended dose of avapritinib is 200 mg orally once daily. Avapritinib is available in 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets, which have a list price of £26,667.00 per pack of 30 tablets. A simple PAS fixed price of [redacted] which equates to a [redacted] discount off the list price has been submitted to NHS England. PAS prices have been modelled in the cost-effectiveness analysis.

Drug acquisition costs for avapritinib, midostaurin and cladribine included in this economic evaluation are summarised in Table 45. List prices for avapritinib 100 mg and 200 mg doses, midostaurin and cladribine were taken from the British National Formulary (BNF).[146] The list prices for the 25 mg and 50 mg avapritinib doses have been submitted to the Department of Health and Social Care (DHSC) and are pending approval.

A one-off cost was applied at the start of the model for patients initiating cladribine, based on the number of courses of treatment reported in Barete et al (2015).[127]

Dose intensity/dose reduction were incorporated into the economic model whenever feasible:

- The relative dose intensity (RDI) was not considered for avapritinib due to patients switching from the 200 mg to 100 mg, 50 mg, or 25 mg dosing packages. Discussions with two consultant haematologists in the UK suggested minimal/no drug wasted is expected for avapritinib and therefore not included in the base case.[2]

- Discussions with clinical experts in the UK indicated that, in their clinical practice, it was estimated that [redacted] of patients would decrease midostaurin dosage to 50 mg twice daily, with [redacted] of patients returning back to the full dosing. Therefore, it was assumed an average of [redacted] of patients would receive the reduced dosage at all timepoints in the model.[2]
- In accordance with NICE TA728, the assessment of drug wastage for midostaurin was integrated into the model. However, given the scarcity of relevant data on wastage, it was omitted from the base-case analysis and explored as a scenario. Drug wastage was calculated by determining the number of opened packs as patients progress through the model.
- Clinicians observed that, in conjunction with midostaurin, [redacted] of patients are prescribed anti-sickness tablets, usually in the form of 8mg ondansetron once a day. The associated additional costs have been accounted for in patients receiving midostaurin; refer to Table 45.for details.[2,38]
- The dose intensity/interruption for cladribine was calculated based on the median cumulative dosage (2.25 mg/kg) and the median number of cycles (3.68) reported in Barate et al (2015). Five vials were calculated per treatment course, including wastage. This is consistent with input gathered from two consultant haematologists in the UK, indicating a recommended dosage of 0.14 mg/kg per administration occurring five times, with an anticipated range of repeat cycles between 3 and 4.[2]

Table 45. Summary of per cycle acquisition costs

Treatment	Strength per pack	Recommended dose per day	Units per pack	Cost per pack	Cost per unit	Units per admin	RDI	Cost per admin	Admins per cycle (monthly)	Cost per cycle (monthly)
Avapritinib	200 mg	200 mg	30	£26,667	£889	1	100%	£889	30.4	£27,056
Midostaurin	25 mg	100 mg	56	£5,610	£100	4	[redacted]	£401	60.9	£24,393
Cladribine	10 mg/5 ml	0.14 mg/kg	1	£165	£165	2	100%	£330	3.68*	£6,072
Ondansetron	8mg	8mg	10	£1.25	£0.13	1	[redacted]	£0.13	60.9	£7.60

Abbreviation: RDI, Relative dose intensity; Admins, Administrations.
*Cladribine is assumed to be used for 3.68 cycles

The dosing schedule assumed for treatments included in the economic model are presented in Table 46. Dosing schedules were based on the SmPC's and discussions with consultant haematologists in the UK.[2]

Table 46. Dosing schedule

Treatment	Avapritinib	Midostaurin	Cladribine
Pharmaceutical formulation	Tablet	Capsule	Vial
Recommended dose per administration	200 mg (starting dose)	200 mg	0.14 mg/kg
Dosing frequency	200 mg once a day	100 mg twice a day	5 times per treatment cycle (1 month)
Units per administration	1	4	2

B.3.6.1.2 Administration costs of intervention and comparators

The cost of administration was taken from NHS reference costs 2021/22 and was based on a previous HTA submission in AdvSM (NICE TA728). Within the NHS reference costs database, each procedure is distinguished by one or more codes, with each code linked to a specific service. Given that many procedures are associated with multiple codes, an aggregate cost was determined using a weighted average. The weight for each service is assigned based on the frequency of administration in 2021/22. Additionally, some treatment modalities are associated with different possible administration procedures, which can vary depending on the single patient characteristics. To account for these differences, the model relied primarily on the same assumptions made in NICE TA728.[42] Table 47 summarises the costs of the administration procedures.

Table 47. Drug administration costs

Administration procedure	Unit costs	NHS reference codes
Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	£435	SB14Z[136]
Deliver subsequent elements of a chemotherapy cycle	£384	SB15Z[136]
Hospitalisation days	£543	SA08G, SA08H, SA08J[136]

As avapritinib and midostaurin are administered orally, administration costs were not included. Cladribine was assumed to be administered intravenously, as discussed with two consultant haematologists.[38] In line with assumptions made in NICE TA728 and clinical

opinion, 65% of patients were assumed to received cladribine in an outpatient setting during the first cycle, while 35% were assumed to be hospitalised for 9 days. In the remaining cycles only 5% of the administrations were assumed to occur in an inpatient setting.[2,42] The one-off administration cost for cladribine sums up to £8,527

Table 48. Cost of pharmacologic therapy - input summary

	Drug acquisition costs	Administration costs	Assumptions
Per cycle costs			
Avapritinib	£27,056	£0	N/A
Midostaurin	£24,393	£0	N/A
One-off costs			
Cladribine	£6,072	£8,527	Assumed 35% of hospitalisations in first cycle and 5% onwards.[2,42]

B.3.6.2 Health state unit costs and resource use

The economic SLR did not identify any costs or resource utilisation associated with AdvSM in the UK. In lieu of this data interviews were conducted with two consultant haematologists clinical experts, relying on information in NICE TA728.[42]

Two UK clinical experts were consulted to estimate the frequency and nature of resource utilisation in patients with AdvSM, distinguishing between those progression-free patients and those with PD. Following the same approach used in NICE TA287, resource utilisation categories were defined based on health states rather than specific treatments, assuming consistent resource requirements regardless of initiated treatment.[42]

The PFS health state was split into 6-monthly cycles (0-6 months, 6-12 months and 12+ months) to capture the frequent resource use associated with monitoring patients in the initial treatment phase. This approach is in line with the previous methodologies applied in NICE HTA submission, TA728.[2,42]

Two consultant haematologists answered the questionnaire, however one clinician found it challenging to respond, noting that answers are contingent on a case-by-case basis. As anticipated, there was some variability in response due to the nature of the disease and absence of UK clinical guidelines. In the base case of the economic analysis, an estimate based on clinician feedback was derived.[2]

Unit costs were derived from NHS reference costs 2021/22 and latest PSSRU published costs.[136,145]

Table 49. Healthcare resource consumption and costs

Resource use	Progression-free			Progressed disease	Unit cost	NHS reference code
	0-6 months	6-12 months	Month 12 onwards	Any cycle		
GP-visit surgery	0.167	0.000	0.000	0.000	£41	PSSRU 2022[145]
District nurse visit	0.000	0.000	0.000	0.000	£54	N02AF [136]
Cancer nurse visit	0.000	0.000	0.000	0.000	£92	N10AF, N10AN, N10CF [136]
Paint and symptom management	0.017	0.017	0.008	0.008	£118	N21AF [136]
Depression management	0.167	0.167	0.083	0.083	£99	A06A1 [136]
Outpatient visits	1.167	0.500	0.333	0.333	£206	WF01B, WF01D, WF02B, WF02D [136]
ED use	0.017	0.000	0.000	0.000	£278	VB01Z, VB02Z, VB03Z,VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z [136]
Hospitalisation days	0.500	0.000	0.000	0.000	£543	SA08G, – SA08J, SA08H [136]
ICU	0.000	0.000	0.000	0.000	£2,144	XC01Z, XC02Z, XC03Z, XC04Z, XC05Z, XC06Z,– XC07Z [136]
Bone marrow biopsy	0.333	0.333	0.250	0.08	£752	SA33Z [136]
ECG	1.167	1.000	0.333	0.08	£363	EY50Z[136]
CT scan	0.333	0.167	0.083	0.08	£142	RD24Z[136]
Chest X-ray	0.167	0.000	0.000	0.08	£142	Assumed to be the same as CT scan, RD24Z[136]
US scan	0.000	0.000	0.000	0.08	£142	RD24Z[136]
MRI scan	0.000	0.000	0.000	0.08	£142	RD05Z[136]
Blood test	1.167	0.500	0.333	0.333	£3	DAPS05[136]

Resource use	Progression-free			Progressed disease	Unit cost	NHS reference code
	0-6 months	6-12 months	Month 12 onwards	Any cycle		
Bone densitometry	0.167	0.167	0.083	0.08	£81	RD50Z[136]

Abbreviations: GP, general practitioner; ED, emergency department; ICU, intensive care unit; ECG, electrocardiogram; CT, computerised tomography; US, ultrasound; MRI, magnetic resonance imaging.

Table 50. Total cost of disease management per heath state

Health state	Total cost
Progression free: 0-6 months	£1,304.50
Progression-free: 6-12 months	£774.30
Progression-free: month 12 onwards	£406.70
Progressive disease	£226.20

B.3.6.3 Adverse reaction unit costs and resource use

The unit costs associated with the management of AEs considered in the economic model are taken from the NHS reference costs 2021/22 and in the case of the drug administration procedures, the aggregate cost of each AE was calculated by averaging the associated NHS codes.[136]

Table 51 summarises the costs associated with AEs.

Table 51. AE related costs

Adverse event	Unit cost	NHS reference code
Thrombocytopenia	£993	SA12G, SA12H, SA12J,SA12K[136]
Anaemia	£917	SA03G, SA03H, SA04G, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J [136]
Other haematological disorders	£1,365	SA08G, SA08H, SA08J [136]
Acute myeloid leukaemia	£4,753	SA25G, SA25H, SA25J, SA25K SA25L, SA25M [136]
Gastrointestinal bleed	£1,695	FD03A, FD03B, FD03C, FD03D, FD03E, FD03F, FD03G, FD03H[136]
Cardiac arrest	£2,382	EB05A, EB05B, EB05C[136]
Non-malignant gastrointestinal tract disorders	£1,844	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M [136]

Adverse event	Unit cost	NHS reference code
Non-malignant hepatobiliary or pancreatic tract disorders	£2,214	GC17A, GC17B, GC17C, GC17D, GC17E, GC17F, GC17G, GC17H, GC17J, GC17K [136]
Cerebrovascular accident, nervous system infections, or encephalopathy	£3,499	AA22C, AA22D, AA22E, AA22F, AA22G [136]
Pneumonia	£2,514	DZ11K, DZ11L, DZ11M, DZ11N DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V, DZ23H, DZ23J, DZ23K, DZ23L, DZ23M, DZ23N [136]
Pleural effusion	£2,303	DZ16H, DZ16J, DZ16K, DZ16L, DZ16M, DZ16N, DZ16P, DZ16Q, DZ16R [136]
Low back pain	£1,187	HC32G, HC32H, HC32J, HC32K [136]
Hypertension	£770	EB04Z [136]
Syncope or collapse	£1,353	EB08A, EB08B, EB08C, EB08D, EB08E [136]
Unspecified oedema	£702	WH10A, WH10B [136]
Tendency to fall senility or other condition affective cognitive functions	£2,145	WH09A, WH09B, WH09C, WH09D, WH09E, WH09F, WH09G [136]
Fever or unknown origin	£1,322	WJ07A, WJ07B, WJ07C, WJ07D [136]
Breast disorders	£781	JA12D, JA12E, JA12F, JA12G, JA12H, JA12J, JA12K, JA12L, JA13A, JA13B, JA13C [136]
Muscular, balance, cranial or peripheral nerve disorders, epilepsy, or head injury	£1,868	AA26C, AA26D, AA26E, AA26F AA26G, AA26H [136]
Sleep disorders	£783	AA43A, AA43B [136]
Other respiratory disorders	£863	DZ19H, DZ19J, DZ19K, DZ19L, DZ19M, DZ19N [136]
Sepsis	£3,084	WJ06A, WJ06B, WJ06C, WJ06D, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J[136]
Heart failure or shock	£2,542	EB03A, EB03B, EB03C, EB03D, EB03E[136]

Adverse event	Unit cost	NHS reference code
Headache, migraine, or cerebrospinal fluid leak	£746	AA31C, AA31D, AA31E [136]
Peripheral vascular disorders	£2,067	YQ50A, YQ50B, YQ50C, YQ50D, YQ50E, YQ50F[136]
Kidney or urinary tract infections	£2,220	LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S [136]
Skin disorders	£1,902	JD07A, JD07B, JD07C, JD07D, JD07E, JD07F, JD07G, JD07H, JD07J, JD07K [136]
Weight increased	£0	-
Appendicitis	£5,182	FF37A, FF37B, FF37C, FF37D, FF37E, FF37F, FF37G[136]
Chronic kidney disorder	£2,872	LA08G, LA08H, LA08J, LA08K, LA08L, LA08M, LA08N, LA08P [136]
Cognitive disorder	£2,145	WH09A, WH09B, WH09C, WH09D, WH09E, WH09E, WH09F, WH09G [136]
Renal failure	£0	-
Non-malignant, ear, nose, mouth throat or neck disorders	£1,273	CB02A, CB02B, CB02C, CB02D, CB02E, CB02F[136]

B.3.6.4 Cost after treatment discontinuation

In PATHFINDER and EXPLORER some patients are reported to interrupt the treatment before progression.[97,102] To reflect this in the model, the cost of cladribine is assigned to a part of the avapritinib treatment arm in a progression free state. Excluding midostaurin treatment cost was deemed as appropriate since it is unrealistic that non-progressed patients who interrupt avapritinib receive midostaurin instead.

In the base case, the PFS curve of the comparator arm is assumed to be the same as the DOT curve. Therefore, no part of the cohort is off treatment before progression.

B.3.6.5 Treatment cost after progression

The part of the cohort entering the progressed disease state is assumed to incur the cost of subsequent therapies. To model this cost, the same assumptions in NICE TA728 was adopted that only 50% of the patients are retreated after progression, this was validated by one consultant haematologist in the UK.[2,42] The correspondent proportion of the cohort in both the avapritinib and the cladribine arms incurs the cost of cladribine. This includes the one-off acquisition and administration costs, as reported in Table 47.

B.3.6.6 Miscellaneous unit costs and resource use

The transition to the death state is associated in the model with a palliative care cost. The costs related to the palliative care for different types of cancer are reported by Round et al.[147] To inform the model, the average of the reported costs has been taken, as summarised in Table 52**.**

Table 52. Costs associated with end-of life

Cancer type	Cost (UK 2014 GBP)
Breast	£7,189
Colorectal	£6,343
Lung	£4,515
Prostate	£9,415
Average	£6,083
2022 inflated costs	£6,836

B.3.7 Severity

AdvSM is a rare debilitating and life-threatening disease.[23,25] Survival varies from time of diagnosis depending on the disease subtype of AdvSM, that is, 2 months for people with MCL, 3 years for people with SM-AHN and 6 years for people with ASM.[23,25]

There is a high unmet need for people living with AdvSM, given that midostaurin is the only NICE recommended therapy for patients with AdvSM. Analysis of OS by Reiter et al,[86] estimated that less than half (49.2%) of patients treated with BAT, including midostaurin, survived beyond 24 months, whilst more than half of patients treated with avapritinib survived beyond 48 months. Given the importance of improving PFS and OS, there remains a clear unmet need for treatments that provide improved efficacy and outcomes for patients with AdvSM. Other than avapritinib, no other therapies potently and selectively targets KIT D816V, the primary underlying driver of the disease.

In line with the updated NICE process and methods, the severity of the condition, measured by QALY shortfall has been calculated to understand the absolute and proportional QALY shortfall associated with current clinical management. Within the new framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within given cut-off ranges (Table 53). A variety of sources have been considered to inform the total expected QALYs of patients with AdvSM treated current clinical management. The following sources were used for current clinical management:

- Method 1: Using baseline characteristics as in base-case economic analysis;
- Method 2: Using baseline characteristics from Sriskandarajah et al.,2021;[37]
- Method 3: Using baseline characteristics from Sperr et al., 2019;[23]

- Method 4: Assessing outcomes associated from prior TA782 appraisal for midostaurin for treating AdvSM.

Table 53: QALY weights referenced within the NICE manual

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12–18	0.85-0.95
x1.7	At least 18	At least 0.95

Abbreviations: QALY, quality adjusted life year.

As referenced by NICE, to estimate the shortfall, the Schneider et al., 2021 estimator tool was used to explore the appropriateness of applying a severity modifier.[148] The tool uses ONS data from England to generate the general population survival. Given NICE DSU indicates that the EQ-5D-3L is a preferred method of capturing utility values, EQ-5DL-3L data from the HSE 2012 and 2014 were used to estimate HRQoL.

Table 54 summarises data used in the Schneider et al tool to calculate the base case QALY shortfall.

Table 54. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
1L patients		
Sex distribution	47% females	See Section B.3.4.1
Starting age	68	See Section B.3.4.1
2L+ patients		
Sex distribution	39% females	See Section B.3.4.1
Starting age	67	See Section B.3.4.1

Abbreviations: QALY, quality adjusted life year; 1L, first line; 2L+, second line plus.

Method 1

Assuming a cohort age of 68 and 47% female distribution for 1L (as per PATHFINDER) and using discounted QALYs for midostaurin from the economic analysis (method 1), the absolute shortfall is estimated to be 7.82, with a proportional shortfall of 79.22%.

Assuming a cohort age of 67 and 39% female distribution for 2L+ (as per PATHFINDER) and using discounted QALYs for BAT (as a proxy for cladribine) and cladribine from the economic analysis (method 1), the absolute shortfall is estimated to be 8.60 and 8.58, with a proportional shortfall of 84.32% and 84.13%, respectively.

The absolute and proportional QALY shortfall values for 1L and 2L+ failed to meet a QALY weighting based on method 1.

Table 55. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Age =68 % of females = 47% QALYs = 9.87	Midostaurin (1L patients): 2.05 (discounted)	Absolute: 7.82 Proportional: 79.22%
Age =67 % of females = 39% QALYs = 10.20	BAT (as a proxy for cladribine, 2L+):1.60 (discounted)	Absolute: 8.60 Proportional: 84.32%
Age =67 % of females = 39% QALYs = 10.20	Cladribine (2L+): 1.62 (discounted)	Absolute: 8.58 Proportional: 84.13%

Abbreviations: BAT, best avaliable therapy; QALY, quality adjusted life year; 1L, first line; 2L+, second line plus.

Method 2

Discussions with leading heamtology consultant in the UK suggested AdvSM age of diagnosis can vary between mid 50s to 60s.[38] Data collected by Sriskandarajah et al., 2021 in UK patients reported a median age of diagnosis for SM was 52, in line with clinical expert feedback.[37] Although the paper references SM, clinical expert in the UK verified that median age of diagnosis was 52 regardless of having ISM or AdvSM and that various prognostic scoring contributes to earlier diagnosis.[38] Therefore, assuming a cohort age of 52 and female sex distibution of 54% and using discounted QALYs for midostaurin for 1L patients, BAT (as a proxy for cladribine) for 2L+ patients and cladribine for 2L+ patients (method 2), the estimated absolute shortfall is estimated to be 13.37, 13.72, 13.70 and with a proportional shortfall of 86.62%, 89.56%, 89.43%, respecitvely.

Within this scenario (method 2), the proportional QALY shortfall meet the x1.2 QALY weighted category, further supporting that a QALY weighting is applicable (see Table 56).

Table 56. Summary of QALY shortfall analysis using baseline characteristics from Sriskandarajah et al.,2021.[37]

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Age =52 % of females = 54 QALYs = 15.32	Midostaurin (1L patients): 2.05 (discounted)	Absolute: 13.37 Proportional: 86.62%

Age =52 % of females = 54 QALYs = 15.32	BAT (as a proxy for cladribine, 2L+):1.60 (discounted)	Absolute: 13.72 Proportional: 89.56%
Age =52 % of females = 54 QALYs = 15.32	Cladribine (2L+): 1.62 (discounted)	Absolute: 13.70 Proportional: 89.43%

Abbreviations: BAT, best avaliable therapy; QALY, quality adjusted life year; 1L, first line; 2L+, second line plus

Method 3

As stated above age of diagnosis ranges between mid-50 to 60s, during the interview the clinical expert recommended to review publication by Sperr et al.,.[38,23] Sperr et al., reported average age of diagnosis for ASM, SM-AHN and MCL, therefore calculating a weighted average of diagnosis of 62 years, in line with clinical expert feedback. [23,38] Therefore, assuming a cohort age of 62 and female sex distribution as in base case and using discounted QALYs for midostaurin for 1L patients, BAT (as a proxy for cladribine) for 2L+ patients and cladribine for 2L+ patients (method 3), the estimated absolute shortfall is estimated to be 9.95, 10.38, 10.36 and with a proportional shortfall of 82.92%, 86.64%, 86.48%, respecitvely.

Within this scenario (method 3), the proportional QALY shortfall meet the x1.2 QALY weighted category, further supporting that a QALY weighting is applicable (see Table 56).

Table 57. Summary of QALY shortfall analysis using baseline characteristics from Sperr et al.,[23]

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Age =62 % of females = 47 QALYs = 12.00	Midostaurin (1L patients): 2.05 (discounted)	Absolute: 9.95 Proportional: 82.92%
Age =62 % of females = 39 QALYs = 11.98	BAT (as a proxy for cladribine, 2L+):1.60 (discounted)	Absolute: 10.38 Proportional: 86.64%
Age =62 % of females = 39 QALYs = 11.98	Cladribine (2L+): 1.62 (discounted)	Absolute: 10.36 Proportional: 86.48%

Abbreviations: BAT, best avaliable therapy; QALY, quality adjusted life year; 1L, first line; 2L+, second line plus

Method 4

The final approach considered using information from NICE TA728. It is noted midostaurin was assessed under the old methodology and achieved end of life criteria. The discounted QALYs for midostaurin were redacted in the submission, however discounted QALYs were available for BAT and disease subgroups The estimated proportional QALY shortfall for all AdvSM and SM-AHN subgroups were 90.53% and 92.69%, respectively. Indicating that a QALY weight of 1.2 is applicable (see Table 58).

Table 58. Summary list of QALY shortfall from previous evaluations.

TA728	Expected total QALYs for general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
All AdvSM patients			
TA728	Age = 63 % of females = 36% QALYs = 11.62	BAT: 1.10	Absolute shortfall: 10.52 Proportional shortfall: 90.53%
SM-AHN subgroups			
TA728	Age = 63 % of females = 36% QALYs = 11.62	BAT: 0.85	Absolute shortfall: 10.77 Proportional shortfall: 92.69%

Abbreviations: BAT, best avaliable therapy; QALY, quality adjusted life year; SM-AHN, systemic mastocytosis with associated haematologic neoplasm.

Although the base case analysis did not meet a severity weighting, alternative methods explored, consistently demonstrated that a x1.2 QALY weight is appropriate for decision making in this appraisal.

Table 59 presents the health state values used to calculate the QALY shortfall analysis.

Table 59. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Progression free (midostaurin 1L)	[redacted]	1.08
Progressed disease (midostaurin 1L)	[redacted]	1.16
Progression free (BAT 2L+)	[redacted]	0.44
Progressed disease (BAT 2L+)	[redacted]	1.35
Progression free (cladribine 2L+)	[redacted]	0.41

Progressed disease (cladribine 2L+)	[redacted]	1.28

Abbreviations: BAT, best avaliable therapy; QALY, quality adjusted life year; 1L, first line; 2L+, second line plus

B.3.8 Uncertainty

Despite implementing all feasible measures to mitigate uncertainty in the analysis, there are several key areas of uncertainty. These are described in the following section along with explanations of how they have been addressed.

B.3.8.1 Uncertainty of clinical inputs

The long-term extrapolations are informed by less than half of the trial population and therefore associated with uncertainty. The long-term extrapolations and comparative efficacy were validated by two UK consultant haematologists.

In the absence of head-to-head trials, uncertainty arises in directly comparing effectiveness of avapritinib to current clinical management. To address this challenge, an ITC comparing real-world outcomes in patients on BAT, including midostaurin and cladribine, collected in the ECS were compared to outcomes in patients treated with avapritinib in PATHFINDER. Eligibility for the BAT cohort were similar to those of the PATHFINDER and rigorous statistical methods (IPTW-weighting and doubly robust estimation) were used to account for the potential differences in the comprehensive list of a priori specified key adjustment covariates between the avapritinib and BAT cohorts. Despite this however, due to the retrospective nature of data collection in the BAT cohort, comparability of the populations and outcomes being compared cannot be guaranteed (see Section B2.9.4.1.)

IPTW uses all available data in the analysis, by assigning weights to each observation, maximising the use of information in the dataset and adjusting for potential cofounding variables. Maximising the data set is particularly useful especially in rare diseases where small sample sizes is a challenge.

The lack of statistical significance observed in the comparison of OS between avapritinib and cladribine in the 2L+ setting is attributed to a small sample size (n=27). To account for the non-significant comparative findings, the analysis with BAT is used as a substitute for cladribine, and this approach was validated by two UK consultant haematologists.[38] It's worth noting that midostaurin contributes over 40% of the BAT basket, and while clinical efficacy is not adjusted for, the efficacy results for cladribine are anticipated to be overestimated. Consequently, the reported results are considered conservative.

As mentioned in Section B.3.4.2.2.3, PFS was unavailable for the comparator due to the nature of defining disease progression in the retrospective observational cohort. Two approaches were considered and aligned with methodology in NICE TA728.[42] The methodology selected by a UK haematology consultant was used in the base case and this was assuming comparator DOT coincides with PFS.[38]

Given the absence of long-term durability studies for evaluating avapritinib, it is assumed the duration of clinical benefit lasts for 5 years. This assumption is based on the DOR reported in PATHFINDER (see Section B.3.4.2.1.4) and has been further investigated in scenario analyses.

Furthermore, the uncertainty in the model were explored through DSA, PSA and scenario analyses, results can be found in Section B.3.12.

B.3.9 Managed access proposal

The PATHFINDER study is ongoing, however current data suggest that the benefit extends in the longer-term and potentially beyond the planned study period. As described in section B.2.6.1.3, in PATHFINDER, as of the latest available data cut-off with >2 years follow-up, median OS has not yet been reached in this population; 80% (84 of 105) patients were alive. In longer-term data from EXPLORER (see Appendix M, Section M3), in which patients received a range of avapritinib doses, with median of 45 months follow-up, median OS has not been reached: 36-month survival was 70%.

Further data collection is not expected to materially impact the assessment of cost effectiveness or reduce any potential uncertainties in cost effectiveness. Further data cut-offs for the PATHFINDER clinical study are planned, with completion expected in 2026, which will provide further evidence on duration of response and overall survival. However, because the single arm phase 2 study will not provide additional comparative evidence, the model would still rely on indirect evidence for comparator treatments, so this would not resolve a potential key uncertainty.

The impact of varying overall survival was assessed by testing the most pessimistic and the most optimistic extrapolations for PFS and OS. The ICER results for the analysis including the avapritinib results were [redacted]. The net monetary benefit (NMB) at a willing to pay threshold of [redacted] per QALY gained varied by around +/-[redacted]% from the base case. It is anticipated that this analysis would have a minimal impact on the ICERs when the commercial agreement is applied for midostaurin.

Therefore, avapritinib is not considered an appropriate candidate for a Managed Access Agreement.

B.3.10 Summary of base-case analysis inputs and assumptions

B.3.10.1 Summary of base-case analysis inputs

A summary of the base-case inputs included in the model are provided in Table 60.

Probabilistic sensitivity analysis was performed for the base case as this accounts for joint uncertainty across most input parameters in the model. The probabilistic analysis is also preferred in the NICE reference case.[123] All parameters were included in the probabilistic analysis, with the exception of time horizon, discount rates and drug costs as these are not subject to parameter uncertainty. Parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques, run with 5,000 iterations for the base-case.

Deterministic analysis was also performed. One-way deterministic sensitivity analysis (DSA) was conducted to evaluate the key drivers in the model. Parameter uncertainty was tested using DSA, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, value ± 1.96×SE. or if unavailable ± 10% where no estimates of precision were available.

Table 60. Summary of variables applied in the economic model

Variable	Value and confidence interval (distribution)			Measurement of uncertainty and distribution	Reference to section in submission
	Comparison A (avapritinib versus midostaurin, 1L)	Comparison B (avapritinib versus BAT, as a proxy for cladribine, 2L+)	Comparison C (avapritinib versus cladribine, 2L+)		
Model setup parameters					
Time horizon	Lifetime (20 years)	Lifetime (26 years)	Lifetime (27 years)	Not varied	See Section B.3.3.3
Cycle length	1 month	1 month	1 month	Not varied	See Section B.3.3.3
Discount rate – costs	0.035 (0.00-0.06)	0.035 (0.00-0.06)	0.035 (0.00-0.06)	Beta	See Section B.3.3.3
Discount rate – QALYs	0.035 (0.00-0.06)	0.035 (0.00-0.06)	0.035 (0.00-0.06)	Beta	See Section B.3.3.3
Patient characteristics					
Age at baseline	68.29 (54.90-81.67)	66.55 (53.51-79.60)	66.55 (53.51-79.60)	Gamma	See Section B.3.4.1
Proportion of males	0.53 (0.423-0.628)	0.61(0.49-0.727)	0.61(0.49-0.727)	Beta	See Section B.3.4.1
Average weight (kg)	71.94 (57.84-86.05)	72.01 (57.90-86.13)	72.01 (57.90-86.13)	Gamma	See Section B.3.4.1
Efficacy (survival distributions)					
OS avapritinib extrapolation	Generalised gamma	Exponential	Exponential	Cholesky	See Section B.3.4.2.1.1
OS comparator extrapolation	Exponential	Weibull	Exponential	Cholesky	See Section B.3.4.2.2.1
PFS avapritinib	Generalised gamma	Log-normal	Log-normal	Cholesky	See Section B.3.4.2.1.3
PFS comparator	Exponential	Exponential	Exponential	Cholesky	See Section B.3.4.2.2.3

Variable	Value and confidence interval (distribution)			Measurement of uncertainty and distribution	Reference to section in submission
	Comparison A (avapritinib versus midostaurin, 1L)	Comparison B (avapritinib versus BAT, as a proxy for cladribine, 2L+)	Comparison C (avapritinib versus cladribine, 2L+)		
DOT avapritinib	Exponential	Exponential	Exponential	Cholesky	See Section B.3.4.2.1.2
DOT comparator	Exponential	Exponential	Exponential	Cholesky	See Section B.3.4.2.2.2
Utility					
PF	[redacted]	[redacted]	[redacted]	Normal	See Section B.3.5.7
PD	[redacted]	[redacted]	[redacted]	Normal	See Section B.3.5.7
Decrement in utility associated with mode of administration					
Cladribine	N/A	-0.074 (-0.089–0.059)	-0.074 (-0.089–0.059)	Normal	See Section B.3.5.6
Drug acquisition costs per cycle unless stated					
Avapritinib	27056	N/A	N/A	Not varied	See Section B.3.6.1.2
Midostaurin	24393	N/A	N/A	Not varied	See Section B.3.6.1.2
Cladribine (one-off cost)	N/A	6072	6072	Not varied	See Section B.3.6.1.2
Drug administration costs					
Avapritinib	0	0	0	Not varied	See Section B.3.6.1.2
Midostaurin	0	N/A	N/A	Not varied	See Section B.3.6.1.2
Cladribine	NA	8527 (6855–10197)	8527 (6855–10197)	Gamma	See Section B.3.6.1.2

Variable	Value and confidence interval (distribution)			Measurement of uncertainty and distribution	Reference to section in submission
	Comparison A (avapritinib versus midostaurin, 1L)	Comparison B (avapritinib versus BAT, as a proxy for cladribine, 2L+)	Comparison C (avapritinib versus cladribine, 2L+)		
Disease management costs					
Per cycle PF, cycles (0-6)	1,304.5 (1048.4-1560.2)	1,304.5 (1048.4-1560.2)	1,304.5 (1048.4-1560.2)	Gamma	See Section B.3.6.2
Per cycle PF, cycles (6-12)	774.3 (622.5–926.0)	774.3 (622.5–926.0)	774.3 (622.5–926.0)	Gamma	See Section B.3.6.2
Per cycle PF, cycles (12+)	406.7 (327–486.5)	406.7 (327–486.5)	406.7 (327–486.5)	Gamma	See Section B.3.6.2
Per cycle progressed	226.2 (181.8–270.5)	226.2 (181.8-–70.5	226.2 (181.8–270.5	Gamma	See Section B.3.6.2
% receiving post-progression treatment	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	Beta	See Section B.3.6.5
Other costs					
End of life cost	6836.1 (5496.3–8176.0)	6836.1 (5496.3–8176.0)	6836.1 (5496.3–8176.0)	Gamma	See Section B.3.6.6

Abbreviations: DOT, duration of treatment; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; PF, progression free; PD, progressed disease; 1L, first line; 2L+, second line plus

B.3.10.2 Assumptions

A summary of all model assumptions and justification is provided in Table 61.

Table 61. Model assumptions

Model input	Assumption	Rationale
Time horizon	Lifetime	Duration is sufficient to capture all benefits and costs of treatments for a chronic disease such as AdvSM, as per NICE reference case.[123]
Perspective	NHS in England and Wales, and PSS	Preference specified in NICE reference case.
Cycle length	1 month	The cycle length is 1 month to capture the costs and events associated with progression of AdvSM.
Efficacy	Direct extrapolation of relatively mature PATHFINDER endpoints (OS and PFS) for the base case	Economic analysis uses the PATHFINDER trial data (September 2022 data cut-off). Two consultant haematologists in the UK validated statistical extrapolations.[38]
	Assume PFS is same as DOT for comparators	No evidence is available for PFS in comparator arm due to the nature of a retrospective observational study. Therefore, it is assumed DOT is the same as PFS, to ensure clinical plausibility this has been validated by a consultant haematologist in the UK.[38].
	RWE used DOT for avapritinib	RWE is used to estimate DOT for avapritinib as it is believed RWE will best reflect the true usage of avapritinib in UK clinical practice.
	Duration of avapritinib clinical benefit	DOR sourced from PATHFINDER was used in the model to capture duration of treatment benefit.
Comparators	Exclusion of imatinib and interferons	Based on UK clinical expert opinion there has been a change in the treatment landscape since the positive recommendation of midostaurin. Therefore, based on conversations with clinicians imatinib and interferons were excluded from the economic analysis.[2]
	BAT comparison as a proxy for cladribine	Exploratory analysis due to non-significance results in cladribine alone comparison. Two consultant haematologists in the UK validated using BAT as a proxy for cladribine due to the limited data available.[38]

Utility	Utility values are assumed to differ by health state and treatment line, but not by treatment arm.	Utility by progression status was selected because progression status was the strongest predictor of patient utility. HRQoL results from PATHFINDER showed lower utility at baseline for those receiving 2L+, as it is assumed they have already experienced disease progression. Utility values were validated by two consultant haematologists in the UK.[38]
	PD utility values sourced from literature	The mapping process required stratifying patients based on progression status. However, with only one data set available, literature was utilised to supplement the missing data, the results were validated by two consultant haematologists in the UK.[38]
Costs	Treatment cost after progression.	Discussions with clinical experts in the UK revealed challenges in reaching a consensus on the proportion of patients retreated during the progressed disease state, as treatments are determined on a case-by-case basis. Guidance from a prior NICE appraisal TA728 indicated 50% of patients are retreated after progression, a validation supported by one consultant haematologist in the UK.[2]

Abbreviations: AdvSM, advanced systemic mastocytosis; RWE, real world evidence; OS, overall survival; PFS, progression free survival; PD, progressed disease; HRQoL, health related quality of life; DOT, duration on treatment.

B.3.11 Base-case results

B.3.11.1 Base-case incremental cost-effectiveness analysis results

The cost-effective analyses of avapritinib versus 1L midostaurin, 2L cladribine, BAT 2L+ (as a proxy for cladribine) using the avapritinib PAS fixed price [redacted] discount) in Table 62. Avapritinib is estimated to have a large health benefit for patients versus all three comparators, generating an additional 2.86 LYs and 2.30 QALYs versus midostaurin, 1.78 LYs and 1.34 QALYs versus BAT 2L+ (as a proxy for cladribine), and 1.29 LYs and 1.23 QALYs versus cladribine. Treatment with avapritinib is expected to decrease the costs of treatment versus midostaurin list price, with incremental costs of [redacted] versus midostaurin, but increase costs versus BAT 2L+ (as a proxy for cladribine) and cladribine, with incremental costs of [redacted] and [redacted] respectively.

The health benefits and costs result in ICER values for avapritinib [redacted] midostaurin, [redacted] versus BAT 2L+ (as a proxy for cladribine), and [redacted] versus cladribine.

The NHB and NMB for avapritinib versus the comparators are presented in Table 63 for the comparison versus avapritinib at PAS price. The NHB of avapritinib at WTP thresholds of £36,000 and £30,000 were estimated at [redacted] and [redacted] versus midostaurin, [redacted] and [redacted] versus cladribine, and [redacted] and [redacted] versus cladribine respectively.

As discussed in section B.3.7, based on the calculated proportional QALY shortfall, this appraisal meets the criteria for the severity modifier with a QALY weighting of 1.2. Results demonstrate that at a WTP of [redacted]/QALY, when applying severity modifier, the NHB is greater than zero versus midostaurin and thus the introduction of avapritinib would increase the overall population health. This demonstrates that avapritinib is a cost-effective use of NHS resources in 1L patients.

Table 62. Discounted base case cost-effectiveness results at PAS price

Technology	Total costs (£)	Tota LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	6.11	4.35	[redacted]	2.86	2.30	[redacted]	[redacted]
Midostaurin	[redacted]	3.24	2.05					
Comparison B: Avapritinib vs BAT (as proxy for cladribine), 2L+								
Avapritinib	[redacted]	4.85	2.94	[redacted]	1.78	1.34	[redacted]	[redacted]
BAT	[redacted]	3.07	1.60					
Comparison C: Avapritinib vs cladribine, 2L+								
Avapritinib	[redacted]	4.04	2.85	[redacted]	1.29	1.23	[redacted]	[redacted]
Cladribine	[redacted]	2.75	1.62					

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, Patient access scheme.

Table 63. Discounted base case NHB and NMB results at PAS price

Technology	Total costs (£)	Tota QALYs	Incremental costs (£)	Incremental QALYs	NHB (WTP £36,000)	NHB (WTP £30,000)	NMB (WTP £36,000)	NMB (WTP £30,000)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	4.35	[redacted]	2.30	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	2.05						
Comparison B: Avapritinib vs BAT (as proxy for cladribine), 2L+								
Avapritinib	[redacted]	2.94	[redacted]	1.34	[redacted]	[redacted]	[redacted]	[redacted]
BAT	[redacted]	1.60						
Comparison C: Avapritinib vs cladribine, 2L+								
Avapritinib	[redacted]	2.85	[redacted]	1.23	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	1.62						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; NMB, Net monetary benefit

B.3.12 Exploring uncertainty

B.3.12.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to capture the overall uncertainty in model parameters and the resulting uncertainty in model results. For this PSA, 5,000 simulations were performed.

For the first line analysis versus midostaurin, the mean PSA results are presented in Table 64. The cost-effectiveness plane and acceptability curve are presented in Figure 43 and Figure 44 respectively. The probabilistic results show some variability in the QALY values for each treatment, however, incremental QALYs and costs are expected to remain relatively stable. The incremental PSA means largely match well to the deterministic mean, showing reasonable levels of variability in the ICER outcomes. Avapritinib is shown to be cost effective versus midostaurin at all WTP thresholds.

Table 64: Probabilistic sensitivity analysis results for 1L avapritinib versus midostaurin

	Cost (£)			QALYs			ICER (£/QALY)
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	
Base case	[redacted]	[redacted]	[redacted]	4.35	2.05	2.30	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	2.09	1.00	2.18	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	3.61	1.76	1.77	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	4.64	2.24	2.50	[redacted]

Figure 43: Cost effectiveness plane for 1L avapritinib versus midostaurin

Figure 44: Cost effectiveness acceptability curve for 1L avapritinib versus midostaurin

For the second line and later analysis versus BAT (as a proxy for cladribine), the mean PSA results are presented in Table 65. The cost-effectiveness plane and acceptability curve are presented in Figure 45 and Figure 46 respectively. The probabilistic results show a similar trend to the 1L analysis, with some variability in the QALY values for each treatment, however, incremental QALYs and costs are expected to remain relatively stable. The incremental PSA means therefore largely match well to the deterministic mean, showing reasonable levels of variability in the ICER outcomes. Avapritinib is shown to be cost-effective in most scenarios at a WTP threshold of [redacted].

Table 65: Probabilistic sensitivity analysis results for 2L+ avapritinib versus BAT (as proxy for cladribine)

	Costs (£)			(QALYs)			ICER (£/QALY)
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	
Base case	[redacted]	[redacted]	[redacted]	2.94	1.60	1.34	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	1.44	0.80	1.27	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	2.19	1.19	0.57	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	3.58	2.11	1.90	[redacted]

Figure 45: Cost effectiveness plane for 2L+ avapritinib versus BAT (as a proxy for cladribine)

Figure 46: Cost effectiveness acceptability curve for 2L+ avapritinib versus BAT (as proxy for cladribine)

For the second line and later analysis versus cladribine, the mean PSA results are presented in Table 66. The cost-effectiveness plane and acceptability curve are presented in Figure 47 and Figure 48 respectively. The probabilistic results show a similar trend to the 1L and 2L versus BAT analyses, with some variability in the QALY values for each treatment, however, incremental QALYs and costs are expected to remain relatively stable. The incremental PSA means therefore largely match well to the deterministic mean, showing reasonable levels of variability in the ICER outcomes. Avapritinib is shown to be cost-effective in most scenarios at a WTP threshold of [redacted].

Table 66: Probabilistic sensitivity analysis results for 2L+ avapritinib versus cladribine

	Cost (£)			QALYs			
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	2.85	1.62	1.23	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	1.37	0.80	1.15	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	2.13	0.98	0.35	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	3.39	2.45	1.83	[redacted]

Figure 47: Cost effectiveness plane for 2L+ avapritinib versus cladribine

Figure 48: Cost effectiveness acceptability curve for 2L+ avapritinib versus cladribine

B.3.12.2 Deterministic sensitivity analysis

DSAs are designed to handle uncertainty of parameters included in the model. Results for the ten most influential parameters identified by univariate sensitivity analysis are presented in Figure 49 for the 1L analysis versus midostaurin, Figure 50 for the 2L+ analysis versus BAT (as a proxy for cladribine), and Figure 51 for the 2L+ analysis versus cladribine. The OWSA's showed similar trends in all three analyses, with the discount rates (for both costs and outcomes) and age at baseline being shown to be the most sensitive parameters to variation. Disease management and cladribine administration costs were also shown to have a small impact on the results.

Figure 49: Tornado diagram for OWSA for 1L avapritinib versus midostaurin

Figure 50: Tornado diagram for OWSA for 2L+ avapritinib versus BAT (as proxy for cladribine)

Figure 51: Tornado diagram for OWSA for 2L+ avapritinib versus cladribine

B.3.12.3 Scenario analysis

Various structural assumptions were examined, encompassing both optimistic and pessimistic exploratory analyses. Table 67, Table 68, and Table 69 provides a summary and results of the different scenarios explored for the different analyses.

For the 1L analysis versus midostaurin, all scenarios showed avapritinib to dominate midostaurin. Using DOT from the PATHFINDER versus ECS analysis is the most pessimistic scenario, with the time on treatment for avapritinib significantly increasing versus the RWE base case. The scenario testing the treatment benefit lasting for 10-years is the most optimistic scenario, with significant health benefits gained in the scenario due to the greater estimated efficacy of avapritinib versus midostaurin.

Table 67. Scenario analysis versus midostaurin 1L

Variable	Base case	Scenario	Rationale	ICER (£/QALY)	NMB (WTP £36,000)
Base case				[redacted]	[redacted]
Population of interest	Safety set	RAC-RE	Exploratory analysis	[redacted]	[redacted]
Patient age at diagnosis	Pathfinder 1L population	52-years from UK study on SM	Study representing 192 patients in the UK	[redacted]	[redacted]
Extrapolation approach	Full parametric, separate statistical models	Treatment effects model	As per NICE DSU recommendation	[redacted]	[redacted]
Avapritinib OS parametric extrapolation	Generalised gamma	Exponential	To explore uncertainty associated with parametric survival curve extrapolations	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]
Avapritinib PFS parametric extrapolation	Generalised gamma	Exponential		[redacted]	[redacted]
		Log-normal		[redacted]	[redacted]
Comparator OS parametric extrapolation	Exponential	Log-normal		[redacted]	[redacted]
		Log-logarithmic		[redacted]	[redacted]
DOT	Avapritinib: RWE Saunders et al[109]	DOT: ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg starting dose vs 1L midostaurin (IPTW sample)	To assess impact of DOT	[redacted]	[redacted]

Comparator PFS	Assumed same as DOT	OS HR	To assess the impact of PFS assumption	[redacted]	[redacted]
Allo-HSCT	Exclude	Include	To assess the impact of allo-HSCT on model results	[redacted]	[redacted]
Midostaurin RDI	Include	Exclude	To assess the impact of RDI	[redacted]	[redacted]
Avapritinib treatment benefit	5 years	1 year	To explore lifetime treatment benefit as clinical experts expressed uncertainty	[redacted]	[redacted]
		3 years		[redacted]	[redacted]
		10 years		[redacted]	[redacted]
PD utility	TLR weighted average	TLR plain average	To assess the impact of using a different methodology to derive utilities	[redacted]	[redacted]

Abbreviations: OS, overall survival; PFS, progression free survival; DOT, duration on treatment; RWE, real world evidence; RAC-RE, Response Assessment Committee Response-Evaluable; ECS, external control study; DSU, decision support unit; 1L, first line; 2L+, second line plus; IPTW, inverse propensity treatment weighting.

For the 2L+ analysis versus BAT (as a proxy for cladribine), using DOT from the PATHFINDER versus ECS analysis was also the most pessimistic scenario, with the time on treatment for avapritinib significantly increasing versus the RWE base case. The scenario testing the treatment benefit lasting for 10-years was the most optimistic scenario, with significant health benefits gained in the scenario due to the greater estimated efficacy of avapritinib versus BAT.

Table 68. Scenario analysis versus BAT 2L+ (proxy for cladribine)

Variable	Base case	Scenario	Rationale	ICER (£/QALY)	NMB (WTP £36,000)

Base case				[redacted]	[redacted]
Population of interest	Safety set	RAC-RE	Exploratory analysis	[redacted]	[redacted]
Patient age at diagnosis	Pathfinder 1L population	52-years from UK study on SM	Study representing 192 patients in the UK	[redacted]	[redacted]
Extrapolation approach	Full parametric, separate statistical models	Treatment effects model	As per NICE DSU recommendation	[redacted]	[redacted]
Avapritinib OS parametric extrapolation	Exponential	Log-logarithmic	To explore uncertainty associated with parametric survival curve extrapolations	[redacted]	[redacted]
		Generalised gamma		[redacted]	[redacted]
Avapritinib PFS parametric extrapolation	Log-normal	Log-logarithmic		[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]
Comparator OS parametric extrapolation	Weibull	Log-logistic		[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]
DOT	Avapritinib: RWE Saunders et al[109]	DOT: ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg starting dose vs 2L+ BAT (IPTW sample)	To assess the impact of DOT	[redacted]	[redacted]
Comparator PFS	Assumed same as DOT	OS HR	To assess the impact of PFS assumption	[redacted]	[redacted]

Allo-HSCT	Exclude	Include	To assess the impact of ALLO-HSCT on model results	[redacted]	[redacted]
Avapritinib treatment benefit	5 years	1 year	To explore lifetime treatment benefit as clinical experts expressed uncertainty	[redacted]	[redacted]
		3 years		[redacted]	[redacted]
		10 years		[redacted]	[redacted]
PD utility	TLR weighted average	TLR plain average	To assess the impact of using a different methodology to derive utilities	[redacted]	[redacted]

Abbreviations: OS, overall survival; PFS, progression free survival; DOT, duration on treatment; RWE, real world evidence; RAC-RE, Response Assessment Committee Response-Evaluable; ECS, external control study; DSU, decision support unit; 1L, first line; 2L+, second line plus; IPTW, inverse propensity treatment weighting.

For the 2L+ analysis versus cladribine, the scenario testing the treatment benefit lasting for 1-year being the most pessimistic scenario and the treatment benefit lasting for 10-years being to post optimistic scenario. This is due to the greater estimated efficacy of avapritinib versus BAT, which therefore significantly impacts the health outcomes when the time on avapritinib treatment benefit is extended or reduced.

Table 69. Scenario analysis versus cladribine 2L+

Variable	Base case	Scenario	Rationale	ICER (£/QALY)	NMB (WTP £36,000)
Base case				[redacted]	[redacted]
Population of interest	Safety set	RAC-RE	Exploratory analysis	[redacted]	[redacted]

Patient age at diagnosis	Pathfinder 1L population	52-years from UK study on SM	Study representing 192 patients in the UK	[redacted]	[redacted]
Extrapolation approach	Full parametric, separate statistical models	Treatment effects model	As per NICE DSU recommendation	[redacted]	[redacted]
Avapritinib OS parametric extrapolation	Exponential	Log-logistic	To explore uncertainty associated with parametric survival curve extrapolations	[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]
Avapritinib PFS parametric extrapolation	Log-normal	Log-logarithmic		[redacted]	[redacted]
		Gompertz		[redacted]	[redacted]
Comparator OS parametric extrapolation	Exponential	Gompertz		[redacted]	[redacted]
		Log-logarithmic		[redacted]	[redacted]
DOT	Avapritinib: RWE Saunders et al[109]	DOT: ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg starting dose vs 2L+ cladribine (IPTW sample)	To assess the impact of DOT	[redacted]	[redacted]
Comparator PFS	Assumed same as DOT	OS HR	To assess the impact of PFS assumption	[redacted]	[redacted]
allo-HSCT	Exclude	Include	To assess the impact of allo-HSCT on model results	[redacted]	[redacted]
	5 years	1 year		[redacted]	[redacted]

Avapritinib treatment benefit		3 years	To explore lifetime treatment benefit as clinical experts expressed uncertainty	[redacted]	[redacted]
		5 years		[redacted]	[redacted]
PD utility	TLR weighted average	TLR plain average	To assess the impact of using a different methodology to derive utilities	[redacted]	[redacted]

Abbreviations: OS, overall survival; PFS, progression free survival; DOT, duration on treatment; RWE, real world evidence; RAC-RE, Response Assessment Committee Response-Evaluable; ECS, external control study; DSU, decision support unit; 1L, first line; 2L+, second line plus; IPTW, inverse propensity treatment weighting.

B.3.13 Subgroup analysis

No subgroup analyses were performed.

B.3.14 Benefits not captured in the QALY calculation

As AdvSM patients are often diagnosed later on in life (mid 50s-60s),[38] it is likely patients would require informal care due to their old age. The QALY is a generic measure which measures solely disease burden for a patient. As a results, it fails to encompass the QoL impacts on particular groups, such as caregivers.

B.3.15 Validation

B.3.15.1 Validation of cost-effectiveness analysis

The model was aligned with NICE's preferred methods. The model was built to align with the NICE reference case and adopted an NHS PSS perspective. The model used a lifetime horizon to capture all costs and QALY gains associated with the intervention.

Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. These procedures included verification of all input data with original sources, programme validation included checks of the model results, calculations, data references, model interface and visual basic for application code.

Wherever feasible, UK consultant haematologist opinion was sought to conceptualise the economic model, ensuring face validity in terms of model structure, inputs and assumptions.

B.3.16 Interpretation and conclusions of economic evidence

AdvSM is a rare debilitating disease with a poor prognosis and short life expectancy. The current treatment in the UK involves current clinical management with only one approved therapy by NICE, midostaurin. Avapritinib has shown superiority in all clinical outcomes compared to midostaurin and cladribine. Also, the demonstrated efficacy of avapritinib suggests that, when combined with allo-HSCT, it provides a potentially curative option for patients with AdvSM.[109] Feedback from a haematology consultant in the UK suggested that allo-HSCT would now be considered earlier on in the treatment pathway with the introduction of avapritinib, further strengthening the unmet need.[38]

The economics analysis is based on a *de novo* economic model with a structure designed to reflect the natural history of AdvSM. The model structure is consistent with NICE committee preferences in TA728.

In line with the NICE process and methods, the severity of the condition was assessed by calculating QALY shortfall to understand the absolute and proportional QALY associated with current clinical management in AdvSM versus general population. Calculations show that this appraisal met the threshold of a QALY weighting of 1.2 in methods listed in section B.3.7.

Base case results demonstrated that avapritinib is cost-effective at the WTP threshold of [redacted]/QALY and [redacted]/QALY [redacted] midostaurin in 1L patients, with a substantial QALY gain of 2.86 associated with [redacted].

The base case results versus cladribine shows avapritinib is associated with [redacted] incremental costs and higher QALYS, resulting in an ICER of [redacted] (versus BAT, as a proxy for cladribine) and [redacted] (versus cladribine, 2L).

In line with the guidance from NICE, both structural and parameter uncertainty have been explored. The robustness of the base case results was assessed via comprehensive probabilistic, deterministic and scenario analyses, with results demonstrating the stability of the base case with a high level of certainty.

Strengths

- The economic analysis is underpinned by a well-designed single-arm trial (PATHFINDER) that is broadly representative of the expected patient population in England and Wales.
- The model structure and assumptions were based on NICE committee preferences stated in TA728 for AdvSM and input from two haematology consultants specialising in treating AdvSM in the UK. Clinicians also validated the clinical plausibility of the long-term survival extrapolations.
- Uncertainty has been explored through various types of sensitivity analysis and results have demonstrated robustness of model and assumptions.

Limitations

- Key limitation of the economic analysis includes the absence of head-to-head trial between avapritinib and current clinical management, which meant that an ITC was used to inform comparator estimates and by default associated with uncertainty.
- Many uncertainties and evidence gaps are inherent in rare diseases such as AdvSM. To address these, various assumptions were made, and to ensure credibility, it was essential to obtain validation for haematology consultants in the UK.

Overall, avapritinib is expected to primarily replace midostaurin in the UK in the 1L treatment setting where it shows [redacted] health benefits and [redacted] costs. Avapritinib addresses an unmet need for a more potent and selective therapy targeting KIT D816V, the primary

underlying driver of the disease. This advancement is reflective in improved response rates and OS compared to currently available therapies.

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B.5 Appendices

Please see separate documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID3770 Avapritinib SIP	V3	No	06 February

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Avapritinib Brand name: Ayvakyt®

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

Advanced systemic mastocytosis (AdvSM) is a term used to describe the most aggressive types of a rare condition called systemic mastocytosis. In this condition, the body produces too many mast cells, a specific type of white blood cell. These excess mast cells build up in different parts of the body, like the skin, organs and bones, leading to symptoms including hot flushes, a forceful or rapid heartbeat, feeling lightheaded, headaches, chest pains or nausea.[1,2] AdvSM is a fatal disease and poor survival estimates have been associated with all forms of AdvSM.[3] Approximately 10% of all systemic mastocytosis cases are classified as AdvSM,[4-6] which includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL).[2] NICE are reviewing the use of avapritinib for the treatment of adult patients with AdvSM, therefore including patients with ASM, SM-AHN and MCL.

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

An application for marketing authorisation for a Type II variation via the national procedure was submitted to the MHRA and, therefore Great Britain marketing authorisation is pending. See Document B, Section B.1.2 for further information on anticipated dates.

Avapritinib has been licensed for use in the European Union since March 2022 as a monotherapy for the treatment of adult patients with ASM, SM-AHN and MCL, after at least one systemic therapy.

In the US, avapritinib is approved by the Food and Drug Administration for the treatment of adult patients with AdvSM.[7]

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

Blueprint Medicines is in broad discussions with The UK Mastocytosis Support Group. The UK Mastocytosis Support Group is a leading patient group in England (Wales and Northern Ireland) supporting research into AdvSM, and care of people living with AdvSM.

Blueprint Medicines has an executed agreement with The UK Mastocytosis Support Group to participate in one international Patient Group Advisory Board through one representative of the Patient Organisation. The meeting took place in November 2023, and the goal was to gather insights into the key challenges faced by the patient community and the patient's perspective on key unmet needs. A fee was provided for this activity and the fees were based on fair market value criteria including a) the time to perform the Services, b) technical complexity of the Services, and c) responsibility assumed by the representative of the Patient Organisation.

Blueprint Medicines also has an existing agreement with The UK Mastocytosis Support Group to participate in two of Blueprint Medicine's Steering Committee Meetings through one representative of the Patient Organisation. Participation in these activities includes reviewing data from the PRISM Survey (an international survey designed to elucidate the burden of disease among European and UK SM Patients) as well as the publications in process stemming from these data with a view to inform additional publication opportunities. Fees will be considered for participation and will b*e* based on fair market value criteria including a) the time to perform the Services, b) technical complexity of the Services, and c) responsibility assumed by the representative of the Patient Organisation.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

AdvSM is a term used to describe the most aggressive types of a rare condition called systemic mastocytosis. In this condition, the body produces too many mast cells, a specific type of white blood cell.[1,2] Mast cells are an important part of the immune system and they help fight infections by releasing signalling chemicals (mainly histamine) into the bloodstream when they detect any allergens.[1,8]

In systemic mastocytosis, mast cells gather in body tissues such as the skin, internal organs and bones. Symptoms are caused when too many mast cells enter various organs of your body and

release these substances such as histamine, which can cause various severe and often unpredictable symptoms (including gastrointestinal, neurocognitive, and systemic symptoms (such as those related to life-threatening anaphylaxis)) as well as damage to involved organs.[1,8-10]

Systemic mastocytosis has a prevalence of ~1:10,000 and an incidence of ~1 in 100,000 person per year.[6] Of those, approximately 10% are classified as AdvSM, which include the most aggressive and life-threatening forms: ASM (~60–70%), SM-AHN (~25%) and MCL (~5–10%).[4-6]

Patients' quality of life is impacted by systemic mastocytosis, particularly when having one of its more advanced forms. The TouchStone survey assessed 56 patients with systemic mastocytosis and found that these patients had a lower quality of life, in both its mental and physical components, compared with people with many other conditions with a high disease burden.[11] Overall, patients with systemic mastocytosis had a similar physical quality of life component score to people with lung cancer and a similar mental component score to people with depression.[11] This indicates that the impact of systemic mastocytosis on patients is severe and is expected to be even more pronounced in the subgroup of patients with AdvSM, which is the population of interest for this submission.

Moreover, AdvSM is a fatal disease and poor survival estimates have been associated with all forms of AdvSM.[3] Patients live in fear due to shortened life expectancy, and the emotional burden of living with the uncertainty of survival has been demonstrated in patients with AdvSM.[12] Other aspects that may impact the quality of life of people with AdvSM include the high number of visits/consultations with health care professionals and reduced work productivity due to severe pain.[11,12]

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

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

The diagnosis of AdvSM and its subtypes is complex. Diagnosis of AdvSM is dependent on a diagnosis of systemic mastocytosis, which is made based on criteria set out by the World Health Organization (WHO) and refined by the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias (ICC).[13-15] An overview of these criteria is provided in Company Submission Document B Section B.1.3.2.

If the criteria for the diagnosis of systemic mastocytosis are met, separate criteria exist to differentiate all three forms of AdvSM:

- Diagnosis of ASM is dependent on identification of one or more clinical signs of organ involvement with organ dysfunction (also known as C-findings).[16-19]
- Diagnosis of SM-AHN depends on the diagnosis of systemic mastocytosis as well as meeting the WHO criteria for an associated haematological neoplasm.[17] Patients with SM-AHN can also present C-findings.
- MCL has even higher levels of mast cell infiltration in the bone marrow compared to systemic mastocytosis. Specifically, the diagnosis of MCL is made when the proportion of mast cells in bone marrow aspirate is demonstrated to be ≥20%. Patients with MCL can also present C-findings.

The treatment being assessed in this appraisal treatment is not expected to change the diagnostic pathway as it does not require any new or additional diagnostic tests.

2c) Current treatment options:

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

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

There are currently no UK-specific guidelines for the management of patients with AdvSM. In the US and Europe, however, the US National Comprehensive Cancer Network and European Competence Network on Mastocytosis have published guidance of the diagnosis and management of patients with SM and mast cell disorders, which includes AdvSM. In these international guidelines, the goals of therapeutic management in patients with SM include the reduction of the potentially severe and often unpredictable symptom burden, reduction of mast cell burden and prolonging survival.[20]

In the UK, midostaurin is the only pharmacological therapy indicated for use in patients with AdvSM, including all three forms of the disease: ASM, SM-AHN and MCL, and is recommended by NICE in this indication.[21] Off-label therapies considered for use in patients with AdvSM in the UK include cladribine, imatinib and pegylated interferon alpha, although these are included as 'other recommended regimens' in the US National Comprehensive Cancer Network guidelines due to lesser efficacy or issues with safety. These off-label treatments are used very minimally in the UK, as was confirmed by clinical experts in England.[22-25] Further information on these treatments can be found in Section B.1.3 in Document B of the submission.

For a small proportion of AdvSM cases, an allogeneic haematopoietic stem cell transplant can be an option. In an allogeneic haematopoietic stem cell transplant, a portion of a healthy donor's stem cells is transferred to the patient. While this can be a curative option for AdvSM patients, numerous eligibility criteria restricts stem cell transplants to approximately 10% of AdvSM patients in the UK.[25] In 2016, experts stated that stem cell transplants should only be considered in patients under the age of 60 who have either a complete matched sibling donor or an unrelated donor with no comorbidities, making them only suitable for a limited subset of patients with AdvSM.[26]

When available, avapritinib is expected to be used to treat patients with AdvSM across all lines of treatment, including as a first-line treatment option.

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

Context:

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

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

The TouchStone SM Patient Survey is a key source of PBE on living with AdvSM.[11] The TouchStone Survey is the first real-world study in systemic mastocytosis to capture patient perspectives on the holistic impact of disease considering quality of life, symptom burden, pain, daily functioning, use of medications, health care services by specialists and work status, and includes a systemic mastocytosis-specific symptom assessment tool.

It should be noted that the TouchStone survey was focused on systemic mastocytosis in general and not solely the AdvSM subtypes, although 9% of participants had ASM and 2% had SM-AHN (which are two of the three AdvSM subtypes).[11]

The TouchStone SM Patient Survey showed that participants reported impaired physical functioning and mental health, decreased work performance and productivity, difficulty completing daily activities and overall poor quality of life, potentially reflecting the chronic nature of the disease. Persistent disability, poor functional status, and frequent anaphylaxis highlight a clear unmet need in this patient population.[11] Moreover, the TouchStone survey demonstrated high systemic mastocytosis-related health resource use, including use of multiple medications for symptom control and numerous visits to multiple specialists.[11]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

People with AdvSM often have changes (mutations) in the genes of their mast cells, most commonly in the genes encoding a type of protein called kinases; a group of proteins that can modify other molecules and hereby change their function and activity. This can lead to a cascade of reactions within the cell that play a key role in big biological processes including the growth and spread of cells.[8]

Avapritinib is a kinase inhibitor, which means it blocks the activity of the protein that signals for cells to multiply. In doing so, avapritinib can help to stop or slow down the excessive growth and spread of mast cells.[8]

3b) Combinations with other medicines

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

- Yes / No

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

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

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

No, the medicine is not intended to be used in combination with other medicines but rather as a monotherapy.

3c) Administration and dosing

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

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

Avapritinib comes in the form of film-coated tablets. Avapritinib tablets should be swallowed whole with a glass of water, on an empty stomach. Patients should not eat for at least 2 hours before and at least 1 hour after taking avapritinib.[8]

The recommended starting dose of avapritinib for the treatment of AdvSM is 200 mg orally once daily.[27] The dose should be adjusted based on safety and tolerability. The recommended dose reductions are as follows:

- first dose reduction 100 mg daily,
- second dose reduction 50 mg daily,
- third dose reduction 25 mg daily.

Treatment with avapritinib is not recommended in patients with a platelet count of $<50 \times 10^9$/L due to risk of bleeding.[8]

3d) Current clinical trials

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

The evidence on how well avapritinib works (its efficacy) and the associated side effects and risks (its safety profile) has been demonstrated in two clinical trials conducted in adults with AdvSM. The two clinical trials, EXPLORER (BLU-285-2101, NCT02561988, completed) and PATHFINDER (BLU-285-2202, NCT03580655, ongoing), are both multicentre, single-arm and open-label studies.

EXPLORER was a Phase 1 dose finding and dose expansion study, in which 69 patients with AdvSM received a starting dose of avapritinib ranging from 30 mg to 400 mg orally once a day until disease progression or unacceptable toxicity. Key endpoints of this study included the maximum tolerated dose, the safety profile and response rate. The results of EXPLORER were published by DeAngelo et al. (2021) and longer-term results with almost 4 years of follow-up were reported in 2022.[28,29] Final study results are expected early in 2024.

The key clinical evidence is based on the Phase 2 PATHFINDER trial, investigating the safety and efficacy of avapritinib in 107 adults with AdvSM. In PATHFINDER, avapritinib is administered at a starting dose of 200 mg orally once daily and key endpoints include response rates and survival rates. PATHFINDER includes one site in England (Guy's and St Thomas' NHS Foundation Trust,

London; nine patients). Interim-data from this trial were published by Gotlib et al (2021), while the latest available data (September 2022 cut-off), were reported in 2023.[30,31] Results from the September 2022 data cut-off in patients who initiated treatment at the 200 mg dose (expected label dose), are used to support the economic model and are described in Section B2.6 of Document B of the evidence submission. The PATHFINDER trial is still ongoing and is planned to be completed in 2026.

Both studies included adults with all subtypes of AdvSM (ASM, SM-AHN or MCL) who were either treatment-naïve (that is, they had not received a previous systemic therapy, a therapy that works throughout the body, for AdvSM) or who had previously received one or more systemic therapies. Eligible patients were required to have an ECOG performance status of 0 to 3, meaning that only those with the most severe functional disability (ECOG status 4) were excluded. Palliative and supportive care medications were allowed during the studies.

3e) Efficacy

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

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

Direct clinical evidence (EXPLORER and PATHFINDER)

Treatment with avapritinib in EXPLORER and PATHFINDER produced rapid, durable responses in adults with AdvSM. Patients experienced reductions in objective measures of mast cell burden, reversion of mast-cell-related organ damage and improvements in symptoms.

In EXPLORER, responses were seen at all starting doses (30–400mg once daily) but occurred most rapidly at doses of at least 200 mg once daily. Review of safety, rapid reduction of disease burden and response rate led to selection of 200 mg as the optimal dose for patients with AdvSM.[8]

In PATHFINDER, there was an overall response rate of 74% in patients treated with 200 mg avapritinib.[32] Responses occurred in most patients in under three months: median time to response was 2.2 months (range: 0.3 to 15 months).[32] Responses were observed irrespective of prior therapy and disease subtype.[32] As of the latest available data cut-off (with >2 years of follow-up) most patients (87%) who demonstrated a response to avapritinib maintained this response. Responses were observed irrespective of prior therapy and disease subtype. [32] As of the latest available data cut-off (with >2 years of follow-up) most patients (52/60) who demonstrated a response to avapritinib maintained this response as of the data cut-off.[32]

Strengthening the demonstration of efficacy, among all patients with AdvSM in PATHFINDER, 24-month survival was estimated at 79% (95% CI: 71,87), with survival by AdvSM subtype reflecting the overall response observations. Median overall survival was not reached, meaning that most patients were alive at the time of the data cut-off and a longer follow-up period is required to determine this.[32]

Indirect comparative analyses

Significant advantages for avapritinib were demonstrated when comparing it to other therapies used for the treatment of AdvSM, including midostaurin.[33,34]

Given the single-arm nature of both avapritinib trials, there is no direct comparison (within trial) of the clinical effects of avapritinib versus those with the other comparator treatments for AdvSM. Therefore, an external control study (BLU-285-2405; NCT04695431) was conducted to generate real-world data on best available therapies, including midostaurin and cladribine, that could be used to compare outcomes in patients treated with avapritinib in the EXPLORER and PATHFINDER trials. Avapritinib treatment in trials resulted in significantly improved overall survival, longer duration of treatment, and greater reduction in serum tryptase (a marker of mast cell burden) compared to midostaurin or cladribine in real-world clinical practice.[33]

A suitable analysis in this case was a matching-adjusted indirect comparison, in which individual patient data from the two avapritinib studies were indirectly compared with data from the two main studies evaluating midostaurin. This analysis in described in Document B of the evidence submission, Section B2.9.3 and was published by Pilkington et al in 2021.[34] In this analysis, the likelihood of demonstrating a response to treatment, including complete remission, was significantly higher for avapritinib when compared to midostaurin.[34] A treatment that improves remission rates and offers an opportunity of complete remission may increase eligibility for stem cell transplantation in AdvSM.[25] In this analysis, avapritinib also produced higher likelihoods of survival compared to midostaurin.[34]

Taken together, the comparison of avapritinib versus other therapies for AdvSM demonstrates that patients receiving avapritinib live longer, respond to treatment at a greater frequency, and remain on treatment for longer periods of time, compared to currently available therapies including midostaurin and cladribine.[34,35]

The indirect comparisons are associated with several limitations, which are discussed in detail in Document B, Section B.2.9.4. While the external control study and matching-adjusted indirect comparison employed strategies to maximise comparability between the populations and reduce uncertainty in the estimates of comparative efficacy, the direct comparability of patients, as well as their management, cannot be ensured.

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

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

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

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

The PATHFINDER study included three patient-reported outcome measures:

- The AdvSM symptom assessment form (AdvSM-SAF) that includes assessment of eight AdvSM domains: abdominal pain, nausea, vomiting, diarrhoea, spots, itching, flushing, and fatigue.[36]
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLC-C30), a 30-item questionnaire that includes five functional domains (physical, cognitive, role, emotional, and social) and a global health status scale of 0 to 100.
- The Patient's Global Impression of Symptom Severity (PGIS), a single item scale that assesses a patient's perception of disease symptoms at a point in time. The PGIS has been

widely used to evaluate a patient's overall sense of whether a treatment has been beneficial.

At baseline, patients demonstrated the presence of symptoms associated with AdvSM, including fatigue and abdominal pain which were the most severe symptoms.[31] Improvement in patients' health-related quality of life with the PGIS was evident as demonstrated by decreases in AdvSM total symptom score from baseline to 72 weeks of treatment as well as improvements in patients' perception of their overall symptom severity.[32]

Quality of life was assessed via a global health status score called EORTC-QLQ-C30. An increase of 21 points was observed with the EORTC-QLQ-C30, indicating improvement in overall health-related quality of life. This improvement from baseline is substantial and is deemed to be clinically important.[37] Improvements were seen across important domains of the EORTC-QLC-C30, including those that assess the ability of a patient to perform physical tasks and fulfil roles of work in addition to how patients function emotionally, cognitively, and socially.[32]

Taken together, the data from patient-perspective–based assessments, demonstrate that avapritinib produced significant benefits in health-related quality of life in patients with AdvSM.[28,31]

3g) Safety of the medicine and side effects

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

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The overall safety database includes 193 patients with AdvSM. In patients with AdvSM, safety profiles were manageable with supportive care and/or dose modifications.[27]

Like all medicines, this medicine can cause side effects, although not everybody gets them.[8] Side effects may include:[8]

<u>Very common (may affect more than 1 in 10 people):</u>

- altered taste
- memory loss, changes in memory, or confusion (cognitive effects)
- diarrhoea
- nausea, retching and vomiting
- change in hair colour
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing decrease in red blood cells (anaemia) and white blood cells

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- bleeding in your brain
- increased tear production
- nose bleed
- shortness of breath
- heartburn
- increased fluid in the abdomen
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- gastrointestinal bleed
- rash
- hair loss
- pain
- weight gain
- changes in the electric activity of the heart
- bruising
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Most serious side effects

Some side effects with avapritinib may be serious. Fatal events of intracranial haemorrhage have occurred in less than 1% of patients with AdvSM (all doses). Intracranial haemorrhage occurred in a total of 4 (3.2%) of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg once daily, regardless of platelet count prior to initiation of therapy. In 3 of these 4 patients with intracranial haemorrhage (a total of 2.4% out of 126 patients) the events were considered to be related to the treatment.[27]

In patients with low platelet counts ($<50 \times 10^9$/L), the risk of intracranial haemorrhagic events is higher and avapritinib will not be initiated. If patients experience any symptoms that are signs of brain bleeds (severe headache, vision problems, severe sleepiness, or severe weakness on one side of the body), treatment may be stopped temporarily. Platelet counts should then be evaluated before restarting treatment and monitored as needed during treatment with avapritinib.[27,38]

A broad spectrum of cognitive effects (including memory loss, changes in memory, or confusion) that are generally reversible (with intervention) can occur in patients receiving avapritinib. Cognitive effects were managed with dose interruption and/or reduction, and 2.7% led to permanent discontinuation of avapritinib treatment.[27,38]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

A key benefit of avapritinib when compared to current treatments is the efficacy of avapritinib. When indirectly comparing the efficacy of avapritinib to that of currently available therapies for AdvSM, the results indicate that patients receiving avapritinib live longer. In addition, results indicate that patients respond to treatment at a greater frequency, which is associated with clinical and pathologic improvements, and remain on treatment for longer periods of time compared to currently available therapies including midostaurin and cladribine.[34,35]

Additionally, the dosing schedule of avapritinib is more manageable compared to that of midostaurin; while both treatments are administered as oral tablets, midostaurin is administered twice daily while avapritinib is administered once daily.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

Like with any treatment, certain side effects are associated with the use of avapritinib, although not everybody gets them. Section 3g summarises these side effects comprehensively.

3i) Value and economic considerations

Introduction for patients:

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

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

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

How the model reflects the condition

Health economic models are important for the NICE appraisal process. They compare the overall cost and health benefits of the new treatment with current care in the NHS over a patient's lifetime. However, health economic models can only make predictions about health benefits of the treatments so assumptions need to be made, such as, for example, how long the treatment effect will last.

A health economic model was built to compare the cost and health benefits of avapritinib with those of current clinical management. Midostaurin is currently the only licensed therapy for the treatment of AdvSM in the UK and recommended by NICE.[21] However, it is noted that off-label therapies such as cladribine are used in patients with high disease bulk.

The health economic model includes patients with an average age of 60+ who have been diagnosed with AdvSM.

The model includes three health states. Health states are a description of a person's health status and different health stages they can encounter at one moment in time within a disease. An individual can move to different health states over time but can only be in one health state at any moment. The model evaluates patients monthly and assess patients whether their disease has progressed or remains stable.

There are three treatment options in the model:

- Avapritinib,
- Midostaurin, or
- Cladribine

Modelling how much treatment extends life

- The model assumes that patients who receive avapritinib live longer than those who receive current treatment options by delaying disease progression.
- Overall survival, progression free survival, time on treatment, adverse events and health-related quality of life results from PATHFINDER were utilised in the health economic model (see section 3e-g). Since the PATFHINDER trial has not concluded, avapritinib is expected to delay disease progression and extend life beyond currently available clinical trial data. The results from PATHFINDER were therefore extrapolated using statistical modelling to up to 30 years, with the results of the extrapolation being consulted and validated by UK clinicians.

Modelling how much a treatment improves quality of life

- Both modelled and trial data demonstrate improved outcomes in individuals treated with avapritinib, showing superior results in achieving a deeper and quicker response compared to midostaurin across all patients.
- Avapritinib is expected to improve quality of life in patients with AdvSM, by delaying disease progression allowing patients to remain in stable disease for longer.

What additional costs will avapritinib bring according to the model?

Avapritinib is not anticipated to incur any additional costs to healthcare resource use.

Uncertainty

- Avapritinib is expected to increase eligibility to allogenic haemopoietic stem cell transplant which is a curative option for patients. Data from PATHFINDER demonstrates the rate of complete remission is unprecedented. However, the data regarding outcomes following treatment with avapritinib and subsequent transplant is limited. Therefore, a conservative approach was taken and explored in a scenario.
- The duration of clinical benefit for avapritinib is based on data from PATHFINDER, as long-term data is not yet available. Blueprint have tested multiple assumptions regarding the durability of avapritinib effect.

Results

Results shows prolonged survival for people treated with avapritinib compared with those treated with current treatment options, by slowing disease progression.

Additional factors

A case for medium severity weighting has been made based on past NICE appraisals, specifically TA782. Severity modifiers help NICE categorise how serious a health issue is and how it influences the value of different healthcare interventions or treatments. TA728 was assessed under the old methodology and achieved end-of-life criteria, which is the highest severity, implying the severity of AdvSM.

3j) Innovation

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

Due to its mechanism of action, potency and clinical effects, avapritinib has the potential to improve eligible patients' lives in clinical practice compared with current options.

As described in Section 3a, avapritinib works by blocking the activity of proteins called kinases. Importantly, avapritinib has been shown to particularly inhibit the action of the kinases with a KIT D816V mutation, which is associated with ~95% of AdvSM patients.[39]

When studying the in vitro (see glossary) activity of avapritinib compared to midostaurin, avapritinib has demonstrated 10-fold greater activity against KIT D816V.[39] While 'in vitro' means that this has been studied in isolated cells in a laboratory dish, indirect treatment comparisons using clinical trial data in patients have shown that avapritinib is more effective in improving clinical outcomes in AdvSM patients compared to currently available therapies including midostaurin (as described in Sections 3e and 3h).[33-35] This improved efficacy is supported by the targeted mechanism of action of avapritinib.

Caregiver and family quality of life is not included in the QALY (see glossary) calculation, besides representing an important unmet need for patients and caregivers. AdvSM is typically a debilitating disease that often affects people of a working age, necessitating that they stop working. Family members often become carers for these patients and as such, AdvSM is often a big source of stress and anxiety for patients, their families and carers. By addressing the

underlying causes and symptoms of the AdvSM, avapritinib provides substantial relief and support to caregivers.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Blueprint Medicines does not believe that the draft remit or scope will exclude people protected by equality legislation. However, it should be noted that, unlike midostaurin, avapritinib does not contain gelatine as an excipient. Inclusion of gelatine can prevent people from receiving treatment due to certain religious or cultural beliefs, particularly those of the Islamic faith for whom this product may not be Halal. Provision of a gelatine-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.[40]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

General information on AdvSM and mast cell diseases:

- The Mast Cell Disease Society: https://tmsforacure.org
- The UK Mastocytosis Support Group: https://ukmasto.org/#gsc.tab=0

Scientific publications and conference abstracts on the efficacy and safety and avapritinib:

- PATHFINDER
  - Gotlib et al., 2021.[31] Interim analysis of PATHFINDER: https://pubmed.ncbi.nlm.nih.gov/34873345/
  - Gotlib et al., 2023.[30] Abstract of the 2-year follow-up of PATHFINDER: https://journals.lww.com/hemasphere/fulltext/2023/08003/p1023__avapritinib_in_patients_with_advanced.922.aspx
- EXPLORER
  - DeAngelo et al., 2021.[28] Results of EXPLORER: https://pubmed.ncbi.nlm.nih.gov/34873347/
  - DeAngelo et al., 2022.[29] An updated analysis of EXPLORER: https://www.blueprintmedicines.com/wp-content/uploads/2022/12/Blueprint-Medicines-ASH-2022-Avapritinib-AdvSM-EXPLORER-Update-Poster.pdf
- External control study
  - Reiter et al., 2022.[35] Analysis of the efficacy of avapritinib versus best available therapy: https://pubmed.ncbi.nlm.nih.gov/35790816/

- Reiter et al., 2022. Analysis of the efficacy of avapritinib versus midostaurin or cladribine:
  - Abstract: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9429350/pdf/hs9-6-0904.pdf
  - Poster: https://www.blueprintmedicines.com/wp-content/uploads/2022/06/Blueprint-Medicines-EHA-2022-Avapritinib-Advanced-Systemic-Mastocytosis-Overall-Survival-Treatment-Comparisons-Poster.pdf

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Allogeneic haematopoietic stem cell transplant:** A transplantation of stem cells from a healthy donor to the patient.
- **C-findings:** Clinical signs that the patient's organs are affected (resulting in organ dysfunction) due to mastocytosis.
- **Health state**: A description of a persons' health status and different health stages they can encounter at one moment in time within a disease. Each health state consists of health benefit measurements and costs. An individual can move to different health states over time but can only be in one health state at any moment in time.
- **Histamine:** Histamine is a signalling chemical that is released by the immune system to send messages between different cells, mainly after detecting a substance that triggers an allergic reaction.
- **In vitro:** A sample from living things that is being studied in isolation (like in a culture dish).
- **Incidence:** The number of newly diagnosed cases of a disease within a particular time period (usually per year).
- **Indirect treatment comparison**: Statistical comparison of data from different clinical trials with treatments of interest used to demonstrate which options can offer more benefit.

This approach is used when direct evidence (such as a single trial including patients receiving each relevant treatment) does not exist.

- **Mast cell:** Mast cells are a type of white blood cell that play an important part in the immune system and help fight infection. They reside in the connective tissues and release chemicals such as histamine into the bloodstream when they detect substances that trigger an allergic reaction.
- **Mastocytosis:** A rare condition caused by an excess number of mast cells gathering in the body's tissues.
- **Prevalence:** The number of disease cases present in a particular population at a given time.
- **Quality-adjusted life years (QALYs):** A QALY is a measure used to assess the value of healthcare interventions and treatments. It combines both quantity (the additional years of life that person gains as a result of medical treatment or intervention) and quality of life (the ability to carry out daily activities and freedom from pain or mental disturbances) gained from a particular intervention.
- **Systemic:** Affecting the entire system – systemic mastocytosis can affect several different organs and tissues throughout the body, whereas cutaneous mastocytosis only affects the skin.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID3770 avapritinib clarification questions to PM for company [noCON] vFINAL 20Mar2023.docx	vFINAL	Yes	20 March 2024

Blueprint Medicines thanks the EAG for their questions and appreciates the opportunity to provide clarification where needed. In addition, following discussion with the committee, Blueprint Medicines has also submitted a revised PAS for consideration during this appraisal and revised the economic analyses accordingly.

Section A: Clarification on effectiveness data

Systematic literature review and searches

A1. The search strategies for clinical evidence in Appendix D combined terms for the condition with the interventions and do not have any search terms for the comparators listed in the inclusion criteria. Please can the company clarify whether relevant evidence was missed as a result?

In the overall submission, the term comparator is used for meaning 'the interventions to be compared to the submission's intervention' (midostaurin and cladribine in this case). Since, in the systematic literature reviews (SLRs), the aim is to identify papers on those 'comparator interventions' (midostaurin and cladribine), the 'submission comparators' go into the intervention list of the SLR eligibility criteria table.

In the decision problem addressed in Document B Table 1, the intervention is avapritinib and comparators midostaurin and cladribine, all of which have comprehensive search terms in the strategy.

It was decided that the searches should be limited to the interventions only, not also to the comparators, as using interventions only was the broader, more inclusive way to search. Adding comparator terms would have excluded additional papers. Publications were filtered manually at the abstract review and full text review stages with regards to comparators. Therefore, no relevant evidence was missed as a result of this strategy decision.

A2. PRIORITY: Real world evidence is part of the inclusion criteria for Appendix D. Please can the company clarify whether any relevant evidence was missed by not searching the following sources: the Central Data Registry of The European Competence Network on Mastocytosis (https://innere-med-1.meduniwien.ac.at/en/unsere-klinischen-abteilungen/haematologie-und-

haemostaseologie/projekte/ecnm-the-european-competence-network-mastocytosis/ecnm-registry/) and the EMA's catalogue of RWD sources (https://catalogues.ema.europa.eu/catalogue-rwd-sources).

To the best of Blueprint Medicines' knowledge, the Central Data Registry of The European Competence Network on Mastocytosis (ECNM) only provides access to their data as part of selected ECNM projects. As such, it was not feasible to include information from this data registry as part of the evidence submission to NICE.

EMA's catalogue: searching mastocytosis or mast in this catalogue gave seven registry results, of which one could be relevant to the evidence submission, the ECNM. This registry website has access issues (appears to have a suspended domain; https://www.ecnm.net/), so we were unable to access this data source. Please see an overview of the results in Table 1 below.

Table 1. EMA catalogue: mastocytosis or mast search results

Search term	Registry	Relevancy	Access?
Mastocytosis	https://catalogues.ema.europa.eu/institution/3331198	Relevant	No
Mast	https://catalogues.ema.europa.eu/institution/3331198	Duplication of above	N/A
	https://catalogues.ema.europa.eu/node/1038/administrative-details:	Population not applicable	N/A
	https://catalogues.ema.europa.eu/node/1433/administrative-details:	Population not applicable	N/A
	https://catalogues.ema.europa.eu/node/1658/administrative-details	Population not applicable	N/A
	https://catalogues.ema.europa.eu/institution/3331151	Population not applicable	N/A
	https://catalogues.ema.europa.eu/node/2677/administrative-details:	Population not applicable	N/A
	https://catalogues.ema.europa.eu/node/2643/administrative-details	Population not applicable	N/A

A3. The methodologies and documentation for the four targeted literature reviews within Appendix P are unusual, unclear and are not to the professional standard of the other search strategies throughout the submission. Please can the company clarify why the literature reviews documented in Appendix P

were not conducted systematically and whether any relevant evidence was missed as a result? The following issues were noted:

> ***a) For all TLRs, the search terms and sources searched are very limited and it's not clear which exact dates the searches were performed so we cannot tell how up to date the evidence is.***
>
> ***b) For the TLR to identify QLQ-C30 to EQ-D mapping algorithm, not all the inclusion criteria were searched for. In addition, the Embase strategies do not list the platform used and have no search syntax – if searched on the Ovid platform, search terms would default to the mp (multipurpose) field code, which is not the same as searching all fields as reported.***

In response to a) and b), the four searches were conducted in the context of informing model parameters. The guidelines reported in NICE DSU Technical support document 13 (TSD13) were adhered to whilst conducting the TLRs.

As stated in TSD13, "*Given that it is not common practice to apply comprehensive, systematic review search methods consistently across the modelling process and given that the model development process requires generally the assimilation of a broad range of information within a short time, the following techniques (…) are suggested as a means of maximizing the retrieval of potentially relevant information and of minimizing the opportunity costs of managing irrelevant information (…) Restricting the number of sources searched, Restricting search terms to within specific fields".*

Following the TSD13 guidelines, a TLR was deemed appropriate as opposed to an SLR. Search terms were defined by balancing the trade-off between maximising comprehensive data and minimising irrelevant data. The objective of these searches was to inform the model parameters.

Additionally, to address the uncertainty surrounding the parameters obtained through the TLRs and their utilisation in the cost-effectiveness model, they were incorporated into sensitivity analyses (both deterministic and probabilistic). This was done to

manage parameter uncertainty and evaluate its potential impact on the base case results.

It's worth noting that there was a two-year gap between the execution of the TLRs and the NICE submission date, ideally requiring an update of the TLRs within the recommended six-month window prior to submission. However, given inquiries regarding the use of estimates derived from these searches in reimbursement processes in other contexts (e.g., identification of the QLQ-C30 to EQ-D mapping algorithm), informal searches were conducted to ensure the continued relevance of the initial TLR results.

c) For the TLR to identify QLQ-C30 to EQ-D mapping algorithm the company document 12 search lines but then appear to have only searched the results of line 11, which is misleading.

Table 1 in CS Appendix P reports all the terms that were considered to build the search lines (see Table 2).

The table was included in the CS Appendix P to uphold transparency, however, not all search lines were included for paper selection purposes. Certain search lines, notably those referenced in line 6 and line7, yielded an excessive number of results. Importantly, as mentioned in CS Appendix P1.1 alternative search combinations would have been considered if the selection from line 11 failed to provide satisfactory results.

Table 2. Search lines for targeted literature search

	Query	PubMed	Embase
#1	qlq c30	4,276	8,724
#2	eortc qlq c30	3,588	7,593
#3	qlq c30 OR eortc qlq c30	4,276	8,724
#4	eq 5d	8,714	16,509
#5	systemic mastocytosis	2,419	4,070
#6	quality of life	415,897	717,625
#7	mapping	432,522	312,100
#8	(qlq c30 OR eortc qlq c30) AND eq 5d	185	531
#9	(qlq c30 OR eortc qlq c30) AND systemic mastocytosis	0	2
#10	systemic mastocytosis AND quality of life	44	114

#11	(qlq c30 OR eortc qlq c30) AND mapping	54	90
#12	(qlq c30 OR eortc qlq c30) AND mapping AND systemic mastocytosis	0	0

Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

d) For the TLR to define the QoL during and after allo-HSCT and the TLR to define HSCT efficacy in AdvSM patients, only MeSH terms and no free-text terms were searched.

This was done to minimise the inclusion of irrelevant papers that would have otherwise been selected for screening. In the TLR, free text search was used to define allo-HSCT in patients with AdvSM.

e) For the TLR to identify health state utility values after AdvSM, it is not clear which search fields have been searched on PubMed.

All fields listed in Table 3 were searched on PubMed. In line with the guidelines reported in NICE DSU Technical Support Document 13, the search terms and the queries were defined to obtain results that were as comprehensive as possible while limiting the number of irrelevant papers.

Note that the same table was also presented in CS Appendix P2.1 of the original submission. A detailed description of the number of retrieved papers, the selection process, and the number of papers selected at each step of the selection process is already provided in CS Appendix P2.2.

Table 3. PubMed search fields

	Query	Results (n)
#1	advanced systemic mastocytosis AND quality of life	7
#2	myelodysplastic syndrome AND quality of life	288
#3	chronic myelomonocytic leukaemia AND quality of life	21
#4	myeloproliferative neoplasms AND quality of life	401
#5	myeloproliferative neoplasms AND relapse AND quality of life	22
#6	acute myeloid leukaemia AND quality of life	369

A4. The description of how the health-related quality of life searches were performed in Appendix H was not included, please can the company provide this?

The details on the health-related quality of life searches are reported on pages 86–102 in Appendix H. The database search terms start on page 96.

A5. Please can the company clarify whether the following are errors in documenting the searches or in searching the databases:

a) ***in Appendices D, G, H and I, the update searches of the Cochrane Library list that it was searched on the Ovid platform. However, the strategies use the syntax for the Wiley platform.***

   This was a reporting error; the Wiley platform was used for the Cochrane Library.

b) ***In Appendix H, there is also an error at line 19 in the update searches of the Cochrane library databases.***

   This was a reporting error; the referencing software changed this line in the appendices document mistaking it for a reference code. The line that was searched was: 1-#18.

c) ***If the databases were searched as documented, please can the company clarify whether any relevant studies were missed as a result?***

   No studies were missed from these reporting errors.

A6. There are inconsistencies in the reporting of the number of studies/reports included in the SLR between the Company Submission (CS), Section B.2.1 and the PRISMA diagrams in Appendix D (Figures 1-2).

a) ***Please confirm that 32 studies with 79 publications were included***

This is correct.

b) ***Please report the number of individual studies from the 7 reports included from the update review.***

The seven publications identified in the update reported on seven different studies. Five were additional publications on studies identified in the original review, and two were on newly identified studies.

A7. Please provide justification as to why the cladribine prospective study (Hermine, 2010) was not included in the submission, as cladribine was an intervention included in the eligibility criteria described in Appendix D, Table 2 and is a comparator as per the NICE scope.

The Hermine 2010 study did not report any of the efficacy endpoints considered for the MAIC analysis, per Table 11 of MAIC report. As such, the Hermine 2010 study was not feasible for inclusion in the MAIC, and therefore was not included in the submission.

A8. Please justify why the following decisions were made on the quality assessment of the PATHFINDER, EXPLORER and ECS study:

a) **For *"Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?"* Please justify your response for the External Control Study**

   We agree this should be changed to no, due to being pooled with data from EXPLORER and PATHFINDER. The previous answer was incorrectly interpreted as the patients were recruited from the same retrospective chart review.

b) **For *"Were trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?",* please justify why your response for the External Control Study**

   We agree this should be changed to no. The previous answer was incorrectly interpreted as the patients were recruited from the same retrospective chart review.

c) **For *"Were losses of patients to follow-up taken into account?",* please justify your response for all three studies.**

Following review each answer should be changed to 'no':

- PATHFINDER: was incorrectly interpreted based on "the interim analysis was triggered when 32 response-evaluable patients in cohort 1 achieved sufficient follow-up", and all 62 were included in the safety.
- EXPLORER: should be changed to no based on Figure 1, showing n=53 primary efficacy population out of 69 patients with AdvSM and received the study drug.
- NCT04695431: should be changed to no based on 20 (12.4%) excluded, due to missing performance status.

A9. Please confirm why the question on power calculations "Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%" was not included in the quality assessment of the studies.

This was an error, answers as follows:

- EXPLORER: yes
  PATHFINDER: yes
- NCT04695431: not applicable, as this was a retrospective analysis of data from prospective trials (PATHFINDER and EXPLORER) and a retrospective chart review.

Clinical Effectiveness Results from PATHFINDER and EXPLORER

A10. Please clarify when results from PATHFINDER September 2023 data cut will become available (stated Q2 2024 – see Table 6)?

Results are available and will be provided at a later date.

A11. Please provide the reasons why patients were not eligible for the RAC-RE population (Table 9 in the CS).

a) ***How many patients were unevaluable based on the mIWG-MRT-ECNM criteria, and why were they not evaluable?***

The pre-specified efficacy analysis was performed as per the modified IWG-MRT-ECNM criteria, which stipulate the presence of evaluable C-findings at baseline. Patients with AdvSM need to have 1 or more modified IWG-MRT-ECNM C-findings at baseline (or have MCL, regardless of C-findings) to be eligible for the RAC-RE population.

As per the most recent PATHFINDER data cut-off (September 2023), 24 patients were unevaluable based on the mIWG-MRT-ECNM criteria.

b) ***How many patients did not have ≥2 postbaseline BM biopsy assessments and had been on study for ≥6 cycles?***

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

c) ***How many patients did not have an EOS visit?***

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

A12. PRIORITY: Please provide all efficacy outcomes besides overall survival for the safety population.

All efficacy analyses conducted in the safety population from the PATHFINDER study have been presented in the company evidence submission. Specifically, overall survival, symptom assessment and HRQoL outcomes are presented for the safety population from PATHFINDER. Other efficacy outcomes, including the primary efficacy analysis and all secondary efficacy analyses related to response, were only assessed in the response-evaluable (RE) population.

A13. In Table 9, the PATHFINDER PPRE population is described, but no data for this population is provided

a) ***Please provide the number of patients and baseline characteristics for the PATHFINDER PPRE population***

Data from the September 2022 data cut-off has been provided alongside this response document. Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

b) ***Please provide the results for the PPRE population for pure pathological response outcomes, TTR, DOR, PFS and OS.***

Data from the September 2022 data cut-off has been provided alongside this response document. Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

A14. Please provide details on the reasons why patients discontinued therapy and discontinued from the study owing to 'investigator decision', 'sponsor decision' and 'other/administrative' (Table 10, page 61-62).

Details on the reasons why patients in the PATHFINDER study discontinued therapy and the study owing to 'investigator decision', 'sponsor decision' and 'other/administrative' are shown in Table 4 below (PATHFINDER safety population, 200 mg starting dose).

Table 4. Details on the reason of discontinuation from therapy or the study for patients in PATHFINDER owing to 'investigator decision', 'sponsor decision' and 'other/administrative' (safety population, 200 mg starting dose)

Reason for discontinuation	Recorded details on reason for discontinuation	n
Discontinuation of treatment		
Sponsor decision[a] (n=5)	[redacted]	
Other/administrative[b] (n=6)	[redacted]	
Discontinuation of study		
Other/administrative[b] (n=5)	[redacted]	

[a] Recorded in the study as 'sponsor request'

[b] Recorded in the study as 'other'

Moreover, in reviewing this clarification question we have noticed an error in Table 10 of the company evidence submission. Please see the corrected table below in Table 5 of the clarification question responses. Please note that Table 5 shows that there were no discontinuations due to 'investigator decision' in the safety population of PATHFINDER (200 mg starting dose). Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

Table 5. Patient disposition in patients treated with 200 mg avapritinib starting dose in PATHFINDER [Corrected Table 10 from CS]

	Safety population			RAC-RE population		
	2L+ (n=67) n (%)	1L (n=38) n (%)	All (n=105) n (%)	2L+ (n=51) n (%)	1L (n=30) n (%)	All (n=81) n (%)
Discontinued from treatment	35 (52.2)	12 (31.6)	47 (44.8)	23 (45.1)	8 (26.7)	31 (38.3)
Continuing on treatment	32 (47.8)	26 (68.4)	58 (55.2)	28 (54.9)	22 (73.3)	50 (61.7)
Discontinued from study	25 (37.3)	9 (23.7)	34 (32.4)	19 (37.3)	6 (20.0)	25 (30.9)
Reasons for discontinuation of treatment						
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE(s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative/other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for discontinuation of study						
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE(s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative/other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiation of another antineoplastic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy, i.e. patients who have not received prior systemic therapy; 2L+, second or later line of therapy, i.e. patients who have received one or more prior systemic therapies; AE, adverse event; AML, acute myeloid leukaemia; RAC-RE, Response Assessment Committee response-evaluable.
Note: The safety population includes all patients in the RAC-RE population.
Source: PATHFINDER Clinical Summary (2022 data cut-off)[2]

A15. The number of patients in the PATHFINDER safety and RAC-RE population who did not have the *KIT* D816V mutation seems to be substantially higher than the proportion stated in the background section. Please comment on whether the smaller proportion of patients with *KIT* 816V mutations is likely to affect response or the patient outcomes in the trial?

Thank you for flagging this issue. Agreeing with the rates presented in the background section, the number of patients with *KIT* 816V mutations was consistently above 94.7% across the analysed populations and pre-treatment status in PATHFINDER, and therefore should not have affected the trial results.

The mutation data presented in the company evidence submission was mistakenly reported as per 'Major or Minor WHO diagnosis criteria by PI, *KIT* mutation'. However, the data should be reported per the central mutation analyses as this is a standardised assessment using high-sensitivity digital droplet polymerase chain reaction (ddPCR), which provides highly reproducible results even at a very low variant allele fraction level. Data on the *KIT* mutation status of patients in the PATHFINDER safety and RAC-RE populations by central assay are summarised in Table 6 (per the published poster Table 1, EHA 2022 poster).

Table 6. Baseline *KIT* D816 mutation status by central assay in patients treated with 200 mg avapritinib starting dose in PATHFINDER

Characteristic	Safety population			RAC-RE Population		
	2L+ (n=67)	1L (n=38)	All (n=105)	2L+ (n=51)	1L (n=30)	All (n=81)
***KIT* D816V, n (%)**	65 (97.0)	36 (94.7)	101 (96.2)	49 (96.1)	29 (96.7)	78 (96.3)

Abbreviations: 1L, first line of therapy, i.e. patients who have not received prior systemic therapy; 2L+, second or later line of therapy; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; RAC-RE, Response Assessment Committee response-evaluable.

A16. PRIORITY: Please provide the proportion of patients in the safety and RAC-RE population who remained on treatment receiving each dose of

avapritinib at 12, 24, 36 and 42 months, as well as median time to treatment discontinuation.

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

IPTW Analysis

A17. As per the NICE TSD 17, please provide justification for using each variable in the population adjustment in the IPTW – this could either be through external quantitative evidence, expert opinion, or systematic review

Key covariates that were included in the population adjustment in the IPTW, independent of standardised differences, were selected a priori during the protocol and statistical analysis plan preparation stage.

Covariate selection was based on the following considerations:

- Covariates that were available in the avapritinib trials (required since otherwise confounding control methods could not be implemented)
- Clinical importance of key prognostic factors or confounders based on published literature and expert opinion, including components of Mutation-Adjusted Risk Score (MARS)[3] and international prognostic scoring system for mastocytosis (IPSM)[4]

Please see Table 7 below for the rationale for each of the covariates included in the IPTW.

Table 7. Comparison of components of MARS and IPSM with key covariates in BLU-285-2405

Covariate included in IPTW	Rationale
Age	Age >60 years is a component of the MARS prognostic score. Age ≥60 years is a component of IPSM prognostic score. Age was included as a continuous variable in BLU-285-2405 to allow for finer adjustment.
Sex	Expert opinion and published literature. Kluin-Nelemans et al.[5] identified sex as a strong independent prognostic factor in systemic mastocytosis. Authors reported that among patients with ASM or SM-AHN, male patients had significantly inferior OS compared to female patients.

Region (North America or Europe)	Expert opinion. There can be differences in treatment availability and healthcare practice that are related to patient's outcome across study sites. Yet, no patient from the avapritinib cohort was from the UK site, one of the sites contributing data for the best available therapy cohort. Adjusting for study sites would result in violation of the positivity assumption. Accordingly, region (US vs. Europe) was included as a covariate.
Performance status as assessed by the ECOG score	Expert opinion. Adjusting for ECOG performance status in cancer studies is important because it helps to account for differences in patients' functional abilities and overall health status, which can significantly impact treatment outcomes, disease progression, and overall survival.
Anaemia (haemoglobin <10 g/dL)	Anaemia as defined by haemoglobin <10 g/dL is a component of the MARS prognostic score.
Thrombocytopenia (platelets <100 ´ 10^9/L)	Thrombocytopenia as defined by platelets <100 × 10^9/L is a component of the MARS prognostic score.
AdvSM subtype (SM-AHN, ASM, or MCL)	Expert opinion and published literature. Studies have reported a median OS of ~3.5 years for ASM, 2 years for SM-AHN, and 0.5–2 years for MCL [6-9]
Presence of skin involvement (including reported mastocytosis in the skin or urticaria)	Skin involvement is a component of the IPSM prognostic score.
Leukocyte count ≥16 × 10^9/L	This is a component of the IPSM prognostic score.
Serum tryptase ≥125 ng/mL	This is a component of the IPSM prognostic score.
Testing and number of mutations within the SRSF2/ASXL1/RUNX1 (S/A/R) panel	Presence of one or two or more high molecular risk gene mutation (i.e., S/A/R) is a component of the MARS prognostic score.
Number of prior LOTs received	Expert opinion. Existing literature suggested that exposure to prior therapy was associated with shortened OS.[8]
Types of prior therapy (TKI therapy, cytotoxic therapy, or biologic or other systemic therapy) received	Expert opinion.

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPSM, international prognostic scoring system for mastocytosis; MARS, Mutation-Adjusted Risk Score; MCL, mast cell leukaemia; OS, overall survival; S/A/R, *SRSF2*/*ASXL1*/*RUNX1* gene panel; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; TKI, tyrosine kinase inhibitor.

A18. Clinical advice to the EAG suggested that the following variables, adjusted for in the MAIC, were deemed to be of high prognostic significance in AdvSM: *KIT* D816V mutation status, bone marrow mast-cell burden and number of C-findings. Please comment on how the omission of these variables may influence the IPTW analysis.

The degree of bias due to uncontrolled confounding from an omitted variable is largely dependent on the following parameters:

1. the association between the omitted variable and the outcome conditional on the treatment and all other covariates included in the model, and

2. the distribution (prevalence) of the omitted variable conditional on the treatment and all other covariates included in the model.

For the observed adjusted hazard ratio of 0.59 (95% CI: 0.36, 0.97, p=0.037) when comparing OS between patients treated with avapritinib versus midostaurin (all lines), to fully explain away this association, the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and OS is 2.24 (the E-value), when adjusting for all the other covariates included in the model.[10,11] The E-value would be 3.78 to fully explain away the observed adjusted hazard ratio of 0.32 (95% CI: 0.15, 0.67, p=0.003) when comparing OS between avapritinib and cladribine (all lines). If the strength of association between the unmeasured confounder and exposure is smaller than the E-value, the strength of the association between the unmeasured confounder and outcome must be larger to fully explain away the estimated effect, and vice versa.

*KIT*D816V mutation status was not adjusted because almost all (>90%) patients in both avapritinib and real-world control cohorts had a KIT mutation, thus the association between *KIT*D816V mutation status and treatment was weak to null. Accordingly, the association between *KIT*D816V mutation status and the outcome such as OS would need to be very strong to fully explain away the observed association between treatment and outcome. Studies of key prognostic factors[1,4] for AdvSM have found no association between *KIT*D816V mutation status and OS.

Unlike in clinical trials, information on bone marrow mast-cell burden and C-findings is often not available in patient's medical records in the real-world setting, resulting in large amount of missing information or underestimation in the real-world controls. Mast cell infiltration >30% (measure of bone marrow mast-cell burden), splenomegaly, and albumin <35% (the latter two were possible C-findings) were considered when developing the MARS score, but were not found to be prognostic of OS, after adjusting for age >60 years, sex, AdvSM subtype, haemoglobin level <10 g/dL, platelet count $<100 \times 10^9$/L, serum tryptase >150 mg/L, alkaline

phosphatase >UNL, aberrant karyotype, and number of S/A/R mutations (0, 1, ≥2). There is a large overlap between covariates adjusted for in our External Control Study and the covariates considered in developing MARS (please see our response to A17 above as well). Accordingly, after accounting for these important covariates, it would be unreasonable to expect a strong association between the outcome and bone marrow mast-cell burden or the number of C-findings to fully explain away the observed relationship between treatment and outcome.

Based on the above, we do not think that further adjustment of *KIT*D816V mutation status, bone marrow mast-cell burden, and number of C-findings, when measured accurately in the real-world setting, would fully explain away the reported association between the treatment and outcomes, after already accounting for the pre-selected covariates.

A19. PRIORITY: Please provide an updated IPTW analysis using the September 2022 PATHFINDER data, and the January 2023 EXPLORER data (see also further clarifications regarding the updated IPTW analysis in question B3).

Data from the most recent PATHFINDER and EXPLORER data cut-offs (September 2023 and January 2023, respectively) will be provided at a later date.

A20. PRIORITY: For each IPTW analysis, including those requested in Question A19, please provide:

- **Odds ratios from the logistic regression analysis used in the doubly robust estimation**
- **Propensity score distributions between the intervention/comparator arms before/after treatment weighting**
- **Distribution of weights applied in each IPTW analysis.**

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

A21. PRIORITY: Please provide the baseline characteristics before/after weighting for the pooled EXPLORER/PATHFINDER population compared to the

External Control Study for all analyses, including those requested in Question A19.

As stated in CS Appendix M.7.1, Table 17 to **Error! Reference source not found.** 19 shows the baseline characteristics before and after IPTW-weighting in the subgroups for overall survival. The standardised differences between avapritinib and the comparators decreased to <10% for most covariates, however some differences remained. Please refer to file 'baseline characteristic tables for DOT analyses' for further detail.

A22. Please comment on the use of the IPTW method using a population with small sample sizes.

During study design and protocol development, sample size calculation for the primary outcome of OS showed a power greater than 85% for a sample size of 150 patients in the external control cohort and 131 patients in the avapritinib cohort (pooled EXPLORER and PATHFINDER, as per 2020 data cut-off), assuming a survival proportion of 53% and 76% at 24 months for controls and avapritinib cohorts, respectively. Doubly robust (DR) estimation that combined IPTW and regression adjustment were applied to conduct the analysis. As noted in the NICE TSD17,[12] DR methods have the advantage that only one of the two models (the treatment model and the outcome model) needs to be specified correctly to be able to identify properly the treatment effect.

When conducting subgroup analyses, the same DR estimation method was applied for consistency and interpretation. In these subgroup analyses where sample sizes were reduced, extreme inverse probability of treatment weights from the propensity score (PS) model for treatment may be of concern. To mitigate this, stabilized weights were used and capped at the 1st and 99th percentiles to reduce variability. In certain cases, categories of some covariates were combined due to small sample size to avoid violations of positivity. Upon review of weight distributions, no extreme weights were observed in the analyses.

There have been studies comparing the performance of various methods for confounding control in the literature. Pirracchio et al.[13] evaluated IPTW and PS matching methods for estimating marginal odds ratios when varying sample size

from 1,000 to 40. The authors reported that no substantial increase in the Type I error rate was observed as the sample size decreased from 1,000 to 40 subjects, and that the relative bias remained inferior to 10%, even with a small sample of 40 patients. In the subgroup analyses conducted in this study, some of effect estimates had a large variance (i.e., wide confidence interval) given the reduced sample sizes, but the potential small loss of efficiency compared to regression adjustment-based analysis can be justified by the double robustness property that DR estimation provided.

A23. PRIORITY: Please justify why the IPTW was preferred for the base-case analysis instead of the MAIC.

The IPTW was chosen for the base-case analysis because individual level patient data were available for the comparative analysis. The use of individual patient data allows for more precise adjustment of baseline characteristics through the estimation of individual treatment probabilities. This can help reduce the risk of bias and confounding compared to aggregate data-based methods like MAIC. The choice of IPTW for the External Control Study was in line with the proposed algorithm for method selection when comparative non-randomised data are available as individual patient data, as presented in the NICE TSD17.[12]

Moreover, the topic of the use of MAIC vs. propensity score matching for the base-case analysis was discussed during the decision problem meeting on 17 November 2023, in which the EAG concluded that propensity score matching was the preferred approach in cases where a MAIC does not offer significant additional evidence.

The decision between using IPTW and unanchored MAIC was driven by feasibility and methodological considerations. As MAIC was only feasible if unanchored, the choice was narrowed down to IPTW versus unanchored MAIC. The selection of IPTW was based on its advantages, including the comprehensive utilisation of available data, flexibility in modelling approaches, and simpler implementation without the need for matching. The IPTW approach efficiently incorporated the entire dataset and assigned weights based on treatment probabilities, leading to more accurate estimates. Its flexibility allowed for exploration of various modelling techniques, adapting to data characteristics and treatment assignment nature. In

contrast, unanchored MAIC, involving additional matching steps, risked overfitting in data-limited scenarios. Therefore, the simplicity and transparency of the IPTW approach, along with its ability to address covariate imbalances directly through weighting, made it the preferred choice for the analysis.

To confirm, the base case included IPTW analyses for OS and DOT outcomes and the MAIC for response rates in a scenario analysis to inform allo-HSCT inputs. Blueprint Medicines clarified during the decision problem meeting that the MAIC does include response rates that will be included in the model, as these can't be obtained from the ECS, but that the ECS will be used for the base-case as these allow for more comparisons. The company's understanding was that the EAG agreed with this approach.

MAIC Analysis

A24. As per the NICE TSD 18, please provide justification for using each variable in the population adjustment in the MAIC – for example, refer to supported by external quantitative evidence, expert opinion, or a systematic review

The following variables were explored as potential prognostic factors to match the avapritinib cohort with the midostaurin cohorts: age, sex, race, ECOG, prior therapy, AdvSM subtype, KIT D816V mutation status, bone marrow mast cell burden, serum tryptase level, and number of C-findings. These were identified from company clinical opinion and trial design and by availability of reported data in both the avapritinib and midostaurin studies. Comparisons of these by trial are shown in Table D of the supplementary appendix of Pilkington et al. (2022)[14] (provided alongside this clarification question response document).

Univariate regression models (Cox proportional hazards model for OS, and logistic regression for ORR and CR) were used to explore the effect on each of the 10 possible prognostic factors listed above. The results of these analyses were shown in Figures B, C, and D in the supplementary appendix of Pilkington et al. (2022)[14] (provided alongside this clarification question response document).

The arbitrary cut-off of p<0.1 was used to identify potential prognostic factors, which enabled us to include parameters with some effect but not too many parameters to make the matching unwieldy. Age, AdvSM subtype and race were used for matching for the OS outcome, and additional variables (ECOG, prior therapy, KIT D816V mutation status, bone marrow mast cell burden) were used in addition to the three for OS for matching for analysis of the CR and ORR outcomes. C-findings were identified as possibly important, but a lack of comparability of definition across the trials was deemed too problematic.

A25. In Section B.2.9.4.2, it is noted that the potential omission of prognostic factors and effect modifiers could introduce bias into the results. Please provide further details on this likely bias, and the implications that this could have on the findings of the MAIC.

It is not possible to predict the direction of potential bias for missed/excluded prognostic factors. In particular, the number of C-findings could be a potential prognostic factor, but the different definitions of this variable between the studies makes it inappropriate to combine and control for. See Table C in the supplementary appendix of Pilkington et al. (2022)[14] for more information (provided alongside this clarification question response document).

A26. PRIORITY: Please provide updated MAIC analyses using the September 2022 PATHFINDER data, and the January 2023 EXPLORER data compared to:

a) ***The pooled midostaurin studies;***

b) ***Only study D2201.***

Updated MAIC analyses using the most recent data cut-offs from PATHFINDER and EXPLORER (September 2023 and January 2023, respectively) will be provided at a later date.

A27. PRIORITY: Please provide the full MAIC reports with full details on all MAIC analyses and results (including those requested in Question A26), including:

- **The method of pooling used for the midostaurin studies**

- **The method of population adjustment (propensity score weighting or regression adjustment)**
- **Baseline characteristics of the studies before/after weighting**
- **The distribution of weights, including the number of individuals assigned zero weight**
- **Effective sample size**
- **An estimate of the likely range of residual systematic error in the adjusted unanchored MAIC**

Pooling of midostaurin was performed in two ways:

- For binary outcomes (ORR and CR), the numerators and denominators of outcomes were simply added.

- For the OS outcome, Kaplan-Meier data were digitised to create pseudo-patient level data (Guyot algorithm), and this pseudo-data was pooled together for analysis.

For baseline characteristics, weighted averages were taken where needed to combine to 2 data sources for midostaurin. Propensity score weights were derived for the avapritinib data to match baseline characteristics to the midostaurin patient summaries.

Effective sample sizes are presented in Tables E, F, G in the supplementary appendix of Pilkington et al. (2022)[14] and in the tables below. Residual systematic error was not captured in the adjusted unanchored MAIC.

Baseline characteristics before and after matching are presented below.

OS outcome

Baseline characteristics

Table 8. Baseline characteristics before and after matching (overall survival outcome)

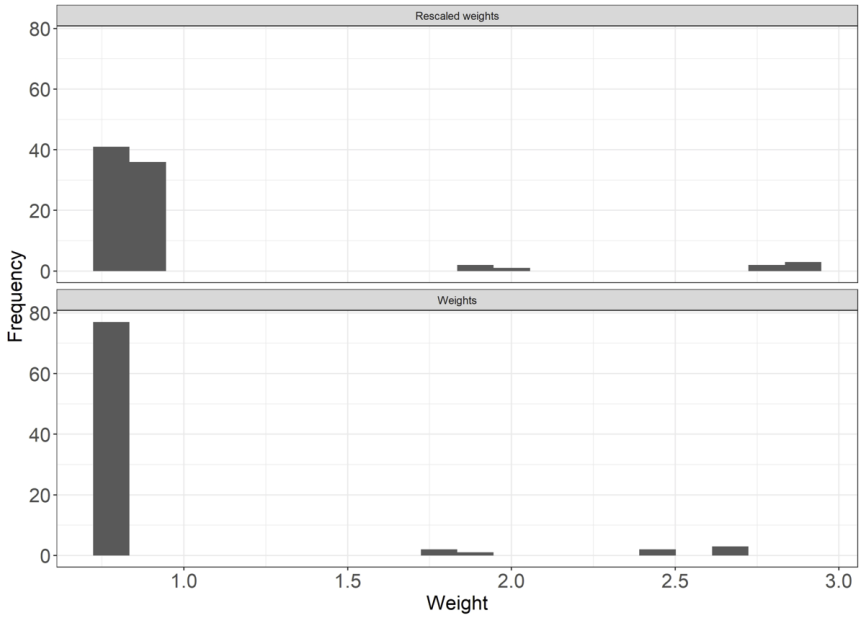
Treatment	Avapritinib (Pooled PATHFINDER & EXPLORER) RAC-RE	Weighted Avapritinib (Pooled PATHFINDER & EXPLORER) RAC-RE	Midostaurin (pooled D2201, A2213) PEP

N/ESS	N=85	ESS=68.1	N=115
Age ≤ median in midostaurin	45%	50%	50%
SM-AHN subtype (%)	74%	64%	64%
ASM subtype (%)	6%	17%	17%
MCL subtype (%)	20%	19%	19%
Race (white %)	96%	93%	93%

Distribution of weights

The smallest (rescaled) weight was 0.82 and the largest was 2.86. 8/85 patients were calculated a weight greater than 1. Please see Figure 1 for a distribution of weights.

Figure 1. Distribution of weights (overall survival outcome)



ORR and CR outcome

Baseline characteristics

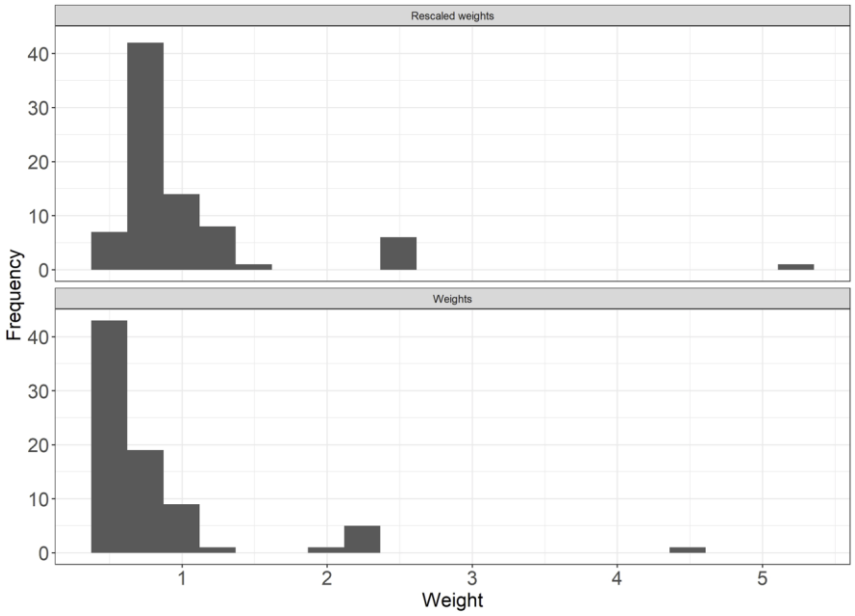
Treatment	**Avapritinib (Pooled PATHFINDER & EXPLORER) RAC-RE**	**Weighted Avapritinib (Pooled PATHFINDER & EXPLORER) RAC-RE**	**Midostaurin (D2201) PEP**

N/ESS	N=79	ESS=53.9	N=89
Age ≤ median in midostaurin	43%	50%	50%
SM-AHN subtype (%)	72%	64%	64%
ASM subtype (%)	6%	18%	18%
MCL subtype (%)	22%	18%	18%
Race (white %)	96%	97%	97%
ECOG 0/1 (%)	66%	64%	64%
KIT_D816 Positive (%)	95%	84%	84%
Bone marrow mast cell ≤ median in midostaurin	54%	50%	50%

Distribution of weights

6/85 patients had zero weight in these binary outcome analyses. The smallest (non-zero) (rescaled) weight was 0.49 and the largest was 5.15. 20/79 patients were calculated a rescaled weight greater than 1. Please see Figure 2 for a distribution of weights.

Figure 2. Distribution of weights (ORR and CR outcomes)



A28. Please provide the supplementary files for Pilkington et al, 2022 (Reference 52 Document B)

This is provided alongside this document (‘Pilkington 2022 supplementary appendix’)

A29. Some of the MAIC analyses compared a subgroup of the avapritinib population to the whole midostaurin population.

a) ***Please comment on the applicability of results from splitting the avapritinib subgroup, but not the midostaurin population;***

b) ***Please comment on whether this causes additional imbalance in population characteristics and how it affects the reliability of the adjustment.***

c) ***Please comment on the plausibility of the assumption that the treatment effect was comparable for patients who did/did not receive prior systemic therapy (as described in Section B.2.9.4.2).***

Updated MAIC analyses using the most recent data cut-offs from PATHFINDER and EXPLORER (September 2023 and January 2023, respectively) will be provided at a later date.

A30. Please conduct an additional MAIC analyses comparing the safety outcomes between patients receiving avapritinib compared to midostaurin, and provide full details as requested in Question A27.

Updated MAIC analyses using the most recent data cut-offs from PATHFINDER and EXPLORER (September 2023 and January 2023, respectively) will be provided at a later date.

Adverse Events

A31. PRIORITY: Please provide adverse event data for midostaurin, cladribine and BAT separately for the ECS.

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

A32. Please provide details of any AEs that led to treatment discontinuation for each of the comparator therapies in the ECS.

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

A33. PRIORITY: Of the patients who experienced a dose reduction in PATHFINDER, please confirm the number of patients who permanently reduced their dose (and what the new dose was), as well as the number of patients who went back to a higher dose after the adverse event resolved and the duration of their dose reduction.

Data from the most recent PATHFINDER data cut-off (September 2023) will be provided at a later date.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness used in the economic model

B1. PRIORITY: Impact of subsequent treatment use on overall survival (OS) when patients discontinue from their initial treatment.

a) ***Please comment on the impact of subsequent treatment use on OS, and clarify whether any adjustment should be made in the analysis for potential confounding of subsequent treatments effects.***

Blueprint Medicines is currently unable to provide this analysis, due to insufficiently reported data in both studies, with a small number of cases inadequate to support any meaningful analysis. In total, there were 10 patients across both studies with partial records. The majority of patients post avapritinib discontinuation pursued transplant options ([redacted]).

UK clinical experts indicated that switching to subsequent therapies is not clinically relevant, with the majority of avapritinib treated patients either continuing with treatment or receiving allo-HSCT. Additionally, for the limited number of patients receiving subsequent therapies like midostuarin due to disease progression or intolerance, the likelihood of experiencing any clinical benefit is low. This is attributed to avapritinib's favourable clinical effect, and it is likely these patients would encounter challenges in tolerating midostaurin as well.[15]

Treatment waning is included in the model for avapritinib which is considered the most pessimistic approach. Data from PATHFINDER 2022 data cut-off demonstrates that duration of treatment benefit is extended to 5 years or more. The KM estimates

for the proportion of patients continuing to respond at 42 months is 70.5% (95% CI; 43.5, 97.4%), suggesting most patients will continue to respond for at least 3.5 years.[73] Therefore, a waning effect has been applied at 5 years in the base case, whereby at 5 years avapritinib efficacy is assumed equal to the comparator arm.

b) Please provide details on what proportion of patients in PATHFINDER (Sept 2022 data cut) and EXPLORER (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) received subsequent midostaurin and subsequent allo-HSCT after discontinuation from avapritinib. Please report separately for each subsequent treatment used, at each line of therapy, and separately for each study.

As stated in B1 a), insufficient data was collected post avapritinib discontinuation. However, of those patients with partial records, [redacted] patients opted for transplant options. Specifically in the PATHFINDER study, there were records for 5 patients, with [redacted] potentially undergoing transplantation and [redacted] receiving alternative treatment. Similarly, in the EXPLORER study, records were available for 5 patients post-avapritinib treatment: [redacted] potentially undergoing transplantations, [redacted] expected to receive cladribine treatment and [redacted] opting for “other treatment options”.

This aligns with similar discussions with leading UK clinical expert, stating approximately 7 or 8 patients have moved to transplant.[16] It’s important to note that UK clinical experts stated avapritinib will increase proportion of patients eligible for transplant and transplant numbers are low but higher now due to avapritinib providing good/deep response rates.[16]

c) Please clarify whether midostaurin is a valid treatment option in the treatment pathway after discontinuation from avapritinib.

Insights from discussions with UK clinical experts indicate that midostaurin would likely be a viable option for only a restricted number of patients, particularly in cases where treatment discontinuation is prompted by non-haematological toxicity.[15] However, as discussed in B1 a), the likelihood of patients achieving clinical benefit with midostaurin post-discontinuing treatment with avapritinib is minimal and therefore not relevant in the treatment pathway.[15]

d) ***Please clarify whether the costs of subsequent treatment use should be included in the model after treatment discontinuation and, if so, please clarify which costs should be considered. Please provide a revised version of the model accordingly and clearly signpost any changes made to the model.***

As discussed in B1 a), UK clinical experts noted that patients receiving first line avapritinib are unlikely to receive subsequent midostaurin.[15] Therefore, as a conservative approach all subsequent costs for midostaurin and avapritinib are set to £0. Updated base case results are presented in Appendix A.

e) ***Please provide Kaplan-Meier curves (with time, proportion of patients alive, and numbers at risk at each time point) for OS for patients in PATHFINDER (Sept 2022 data cut) and EXPLORER (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) who received subsequent midostaurin after avapritinib.***

Insufficient data was collected in the trial to provide this analysis.

B2. PRIORITY: Impact of prior midostaurin use on survival outcomes.

a) ***Please comment on the effects of prior use of midostaurin on survival outcomes in the second and subsequent line (2L+) population setting, and clarify whether any adjustment should be made in the analysis for the potential effects of prior midostaurin use.***

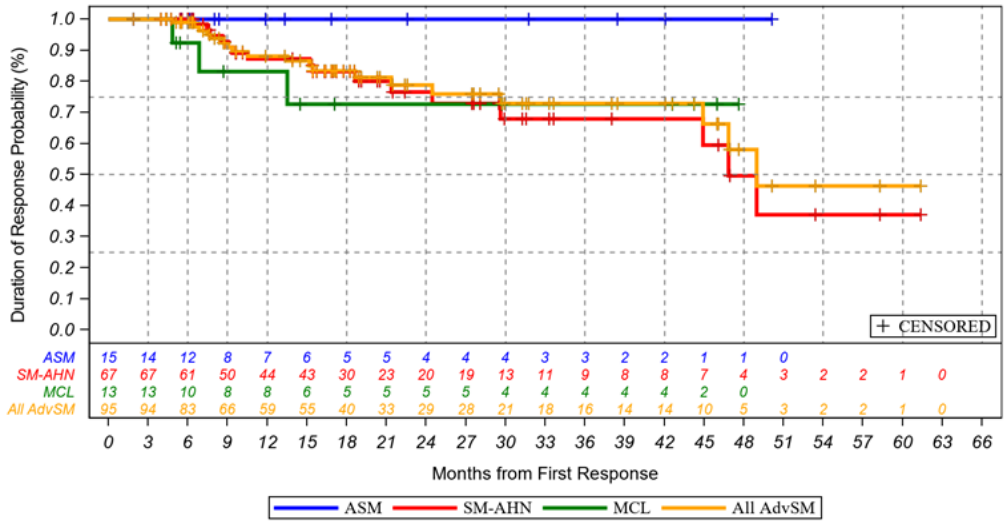
Subgroup analyses of the prior use of midostaurin were performed on the pooled analysis with EXPLORER and PATHFINDER (2021 data cut-offs).[17]

These results indicate that, for all patients in the AdvSM population not previously treated with midostaurin, median OS was 49.0 months (95% confidence interval: 44.9, NE), with 76 (80.0%) of the 95 patients alive at the time of the data cut-off. The Kaplan-Meier estimates for the proportion of patients alive were 100.0% at 3 months and 58.0% at 48 months. Among patients previously treated with midostaurin, median OS was not reached, with 66 (81.5%) of the 81 patients alive at the time of

the data cut-off. The Kaplan-Meier estimates for proportion of patients alive were 93.8% at 3 months to 65.7% at 48 months.[17]

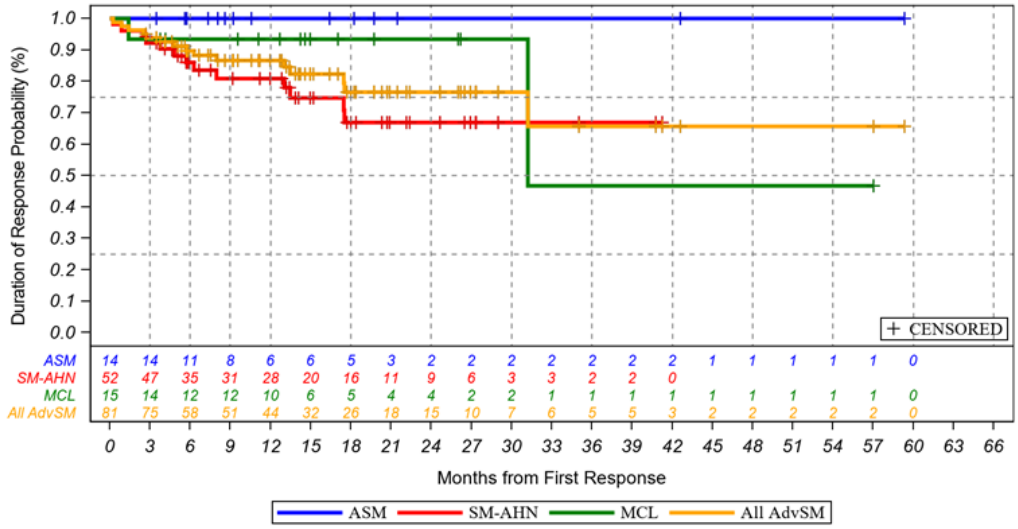
Results between the two subgroups were generally similar for all AdvSM subtypes, with the exception that the median OS was 46.9 months (95% confidence interval: 24.5, NE) in patients with SM-AHN not previously treated with midostaurin. Kaplan-Meier survival curves of OS by prior midostaurin treatment are provided in Figure 3 (patients without prior midostaurin treatment) and in Figure 4 (patients with prior midostaurin treatment) for the AdvSM population.[17]

Figure 3. Overall survival in patients without prior treatment with midostaurin (AdvSM population, pooled EXPLORER and PATHFINDER, 2021 data cut-off)



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm.
Source: MHRA Summary of Clinical Efficacy 2.7.3.[17]

Figure 4. Overall survival in patients with prior treatment with midostaurin (AdvSM population, pooled EXPLORER and PATHFINDER, 2021 data cut-off)



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm.
Source: MHRA Summary of Clinical Efficacy 2.7.3.[17]

Moreover, discussions with UK clinical experts highlighted survival in further treatment lines is expected to be lower not only due to effect of medication but also due to disease progression being further down the pathway and patients not responding to treatment as well.[15]

b) Please provide details on what proportion of patients in PATHFINDER (Sept 2022 data cut) and EXPLORER (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) received prior midostaurin. Please report separately for each study.

See Table 9 for the proportion of patients treated with prior midostaurin for both PATHFINDER and EXPLORER.

Table 9. Proportion of patients receiving prior midostaurin in PATHFINDER and EXPLORER and on 200 mg avapritinib starting dose

Study	PATHFINDER (September 2022 data cut-off)[2]		EXPLORER (January 2023 data cut-off)[18]	
Prior systemic therapy	Safety population	RAC-RE population	Safety population	RAC-RE population
	2L+ (n=67)	2L+ (n=67)	2L+ (n=21)	2L+ (n=17)

Midostaurin, n (%)	56 (83.6%)	41 (80.4%)	10 (47.6%)	10 (58.8%)

Abbreviations: 2L+, second or later line of therapy, i.e, patients who have received one or more prior systemic therapies; RAC-RE, response assessment committee response-evaluable.
Sources: PATHFINDER clinical summary (2022); EXPLORER CSR (2024).[2,18]

c) Please clarify why a comparison of avapritinib with midostaurin is not considered in the 2L+ population setting.

Discussions with clinical experts in the UK highlighted that this is not commonly done in a real-world setting and, as such, this is not clinically relevant.[15]

The clinical experts added that a selective KIT inhibitor such as avapritinib is preferred in clinical practice over other available options due to its increased efficacy compared to other available options.[15] Furthermore, as discussed in B1 a), if patients discontinued 1L avapritinib treatment due to disease progression or adverse events leading to intolerance, it is probable that these individuals would face difficulties tolerating midostaurin.[15]

Although one clinical expert indicated that they may attempt treatment with midostaurin when lacking in other options (even though there are very slim chances of success), overall, the clinical experts stated that midostaurin would likely only be a valid option in a very small minority (for instance in patients that discontinued treatment due to non-haematological toxicities).[15] Therefore, the comparison of avapritinib with midostaurin in 2L+ is excluded in the CS.

d) Please clarify why a comparison of avapritinib with BAT (excluding midostaurin) is not considered in the 2L+ population setting.

Whilst statistically significant improvements in survival were seen when comparing 1L treatment to midostaurin, an updated analysis comparing 2L+ avapritinib and 2L+ cladribine did not reach statistical significance. As noted in the company submission (Section 2.12.2), this may be, in part, be due to the small numbers of patients treated with cladribine (n=23) included in the analysis. The analysis that included all 2L+ best available therapies used in the ECS resulted in a statistically significant improvement in OS with 2L+ avapritinib and was considered to provide a reasonable proxy for current therapies used to treat AdvSM following previous systemic therapy.

Out of the 89 lines of therapy included in the BAT 2L+ cohort with available agent-level information, common therapies included midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%).

Therefore, while an analysis excluding midostaurin could have been completed, this would also be based on a smaller number of patients and treatment lines.

e) Using the comparative data from BAT that included midostaurin as a proxy for cladribine efficacy in the economic model is believed to be a conservative approach. Please provide Kaplan-Meier curves (with time, proportion of patients alive, and numbers at risk at each time point) for OS, progression free survival (PFS) and time on treatment (ToT) for patients in PATHFINDER (Sept 2022 data cut) and EXPLORER (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) in the 2L+ population setting, separately for

i. Patients who received prior midostaurin; and

Figure 5 and Figure 6 are Kaplan-Meier (KM) curves for OS and PFS, respectively, among patients in the 2L+ setting treated with prior midostaurin using pooled EXPLORER and PATHFINDER 2023 data cut-offs. KM curves are not available for ToT.

Figure 5. Kaplan-Meier curves for overall survival in patients who received prior midostaurin (pooled analysis EXPLORER April 2023 data cut-off and PATHFINDER September 2023 data cut-off, safety population,200mg starting dose, 2L+)

Figure 6. Kaplan-Meier curves for progression free survival in patients who received prior midostaurin (pooled analysis EXPLORER April 2023 data cut-off and PATHFINDER September 2023 data cut-off, RAC-RE, 200mg starting dose, 2L+)

ii. Patients who did not receive prior midostaurin.

Figure 7 and Figure 8 are KM curves for OS and PFS, respectively, among patients in 2L+ setting who did not receive prior midostaurin using pooled EXPLORER and PATHFINDER 2023 data cut-offs. KM curves are not available for ToT.

Figure 7. Kaplan-Meier curves for overall survival in patients who did not receive prior midostaurin (pooled analysis EXPLORER April 2023 data cut-off and PATHFINDER September 2023 data cut-off, safety population, 200mg starting dose)

Figure 8. Kaplan-Meier curves for progression free survival in patients who did not receive prior midostaurin (pooled analysis EXPLORER April 2023 data cut-off and PATHFINDER September 2023 data cut-off, RAC-RE, 200mg starting dose,2L+)

B3. PRIORITY: Using data from the EXPLORER study combined with the PATHFINDER study to inform the cost-effectiveness of avapritinib.

a) ***For the combined data from the EXPLORER study (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) and PATHFINDER (Sept 2022 data cut, All AdvSM safety population, 200 mg avapritinib starting dose), and for each treatment comparison in the 1L and 2L+ population settings, please provide the following:***

    i. ***Adjusted Kaplan-Meier curves with comparative data from the ECS (IPTW sample) for OS for avapritinib and the comparators, with parametric goodness of fit measures and corresponding extrapolation curves, i.e., comparisons A, B and C of Section B.3.4.2.1.1 for avapritinib and comparisons A, B and C of Section B.3.4.2.2.1 for comparators.***

Adjusted Kaplan Meiers with comparative data from ECS (IPTW sample) for OS for avapritinib and the comparators using the most recent PATHFINDER data cut-off (September 2023) and pooled PATHFINDER data cut-off (September 2023) and EXPLORER (April 2023) will be provided at a later date.

ii. ***Adjusted Kaplan-Meier curves with comparative data from the ECS (IPTW sample) for time on treatment (ToT) for avapritinib and the comparators, with parametric goodness of fit measures and corresponding extrapolation curves, i.e., as presented in the worksheets 'ToT_AVA' and 'ToT_COMP' in the model.***

Adjusted Kaplan Meiers with comparative data from ECS (IPTW sample) for ToT for avapritinib and the comparators using the most recent PATHFINDER data cut-off (September 2023) and pooled PATHFINDER data cut-off (September 2023) and EXPLORER (April 2023) will be provided at a later date.

iii. ***Please provide a revised version of the model incorporating the data from i) and ii), and with sufficient flexibility to switch between alternative sources of data. Please signpost the changes made to the model.***

An updated model with the revised data will be provided at a later date.

iv. ***Please provide a revised set of cost-effectiveness results that incorporate the data from i) and ii), and uses the ToT curve as a proxy for the PFS curve for both avapritinib and the comparators.***

Updated cost-effectiveness results will be provided at a later date.

b) ***For the combined data from the EXPLORER study (patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available]) and PATHFINDER (Sept 2022 data cut, All AdvSM safety population, 200 mg avapritinib starting dose), please provide an analysis for all-treatment-lines (with adjustment for line of treatment in the IPTW sample), i.e., similar to the all-treatment-line analysis presented in Section B.2.9.2.4.1 of CS. For the all-treatment-line analysis, please provide the following:***

i. ***Adjusted Kaplan-Meier curves with comparative data from the ECS (IPTW sample) for OS for avapritinib and the comparators,***

with parametric goodness of fit measures and corresponding extrapolation curves.

Adjusted Kaplan Meiers with comparative data from ECS (IPTW sample) for OS for avapritinib and the comparators for all treatment lines using the most recent PATHFINDER data cut-off (September 2023) and pooled PATHFINDER data cut-off (September 2023) and EXPLORER (April 2023) will be provided at a later date.

ii. Adjusted Kaplan-Meier curves with comparative data from the ECS (IPTW sample) for time on treatment (ToT) for avapritinib and the comparators, with parametric goodness of fit measures and corresponding extrapolation curves.

Adjusted Kaplan Meiers with comparative data from ECS (IPTW sample) for ToT for avapritinib and the comparators for all treatment lines using the most recent PATHFINDER data cut-off (September 2023) and pooled PATHFINDER data cut-off (September 2023) and EXPLORER (April 2023) will be provided at a later date.

iii. Please provide a revised version of the model incorporating the data from i) and ii) for the all-treatment-line analysis, and with sufficient flexibility to switch between alternative lines of data. Please signpost the changes made to the model.

An updated model with the revised data will be provided at a later date.

iv. Please provide a new set of cost-effectiveness results that incorporate the data from i) and ii) for the all-treatment-line analysis, and uses the ToT curve as a proxy for the PFS curve for both avapritinib and the comparators.

Updated cost-effectiveness results will be provided at a later date.

Duration of treatment

B4. Please justify the use of data based on a small cohort of 13 patients from the Compassionate Use Program (CUP) in the UK to inform duration of

treatment with avapritinib rather than the ToT curves from PATHFINDER in the IPTW analysis of the external control study (ECS).

The comparator arm was subject to a similar approach using real-world evidence, therefore, to ensure a relevant comparison, RWE (CUP) for avapritinib was used in the cost-effectiveness analysis, which was recommended by a UK clinical expert.[16] The CUP was collected in patients from the UK who received avapritinib in clinical practice and therefore this was deemed appropriate for calculating duration on treatment (DOT). It is important to note one UK clinical expert stated overall response rate (ORR) in CUP was reflective of PATHFINDER.

Adverse events

B5. The incidences of adverse events associated with avapritinib in the model are based on data from PATHFINDER (Sept 2022 data cut-off, All AdvSM safety population, 200 mg avapritinib starting dose).

a) ***Please provide cycle probabilities of grade 3+ adverse events based on combined data from PATHFINDER and EXPLORER (for patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available], i.e., similar to Table 41 of CS for the combined studies.***

Table 10. Cycle probabilities of grade 3+ AEs, avapritinib (pooled data, PATHIFNDER 2023 and EXPLORER 2023)

	Avapritinib (pooled data, PATHFINDER 2023 and EXPLORER 2023)
Thrombocytopenia	[redacted]
Anaemia	[redacted]
Other haematological disorders	[redacted]
Gastrointestinal bleed	[redacted]
Acute myeloid leukaemia	[redacted]
Sepsis	[redacted]
Heart failure or shock	[redacted]
Cardiac arrest	[redacted]
Cerebrovascular accident, nervous system infections, or encephalopathy	[redacted]
Haemorrhagic cerebrovascular disorders	[redacted]
Non-malignant gastrointestinal tract disorders	[redacted]

	Avapritinib (pooled data, PATHFINDER 2023 and EXPLORER 2023)
Non-malignant hepatobiliary or pancreatic disorder	[redacted]
Pneumonia	[redacted]
Pleural effusion	[redacted]
Low back pain	[redacted]
Hypertension	[redacted]
Syncope or collapse	[redacted]
Unspecified oedema	[redacted]
Tendency to fall, senility or other condition affective cognitive functions	[redacted]
Fever of unknown origin	[redacted]
Breast disorders	[redacted]
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	[redacted]
Sleep disorders	[redacted]
Other respiratory disorders	[redacted]
Headache, migraine or cerebrospinal fluid leak	[redacted]
Peripheral vascular disorders	[redacted]
Kidney or urinary tract infections	[redacted]
Skin disorders	[redacted]
Weight increased	[redacted]
Appendicitis	[redacted]
Chronic kidney disease	[redacted]
Cognitive disorder	[redacted]
Renal failure	[redacted]
Non-malignant, ear, nose, mouth, throat or neck disorders	[redacted]

b) Please provide a revised model with cycle probabilities of grade 3+ adverse events based on combined data from PATHFINDER and EXPLORER. Please signpost the changes made to the model.

Model has been updated to incorporate pooled AEs from PATHFINDER 2023 and EXPLORER 2023. Updated base case results are presented in Appendix A.

Health-related quality of life

B6. PRIORITY: Health-related quality of life data from EXPLORER (for patients who received 200 mg OD in the January 2023 data cut [or April 2021 data cut, if most recent data cut is not available].

a) Please clarify how much health-related quality of life (HRQoL) data are available from EXPLORER, e.g., please provide details on the time points of assessment using EORTC QLQ-C30 and the number of patients providing EORTC QLQ-C30 data at each time point.

Analysis on 2023 EXPLORER HRQoL will be provided at a later date. The current response provides the HRQoL which was available at the time of the CS.

Please see below the details on numbers of patients providing EORTC QLQ-C30 data at each time point at the time of the CS, stratified by number of visits in the safety 200mg dose population, using the dimension “AVISIT”.

The full safety population with ASM, SM-AHN and MCL totals 69 patients. The following filters were applied to the dataset: a) PARCAT1 =” EORTC QLQ-C30”, b) PARAMTYP=” DERIVED” and c) ANL01FL=” Y”. After filtering, the dataset included 398 observations from 46 patients. Four observations from four different patients had one or more domains missing. Only those patients receiving 200mg dose were included in the analysis, this further reduced the data set to 127 observations from 16 patients. The avapritinib dose of each patient was taken from the ADSL dataset (variable “TR01PG1”).

EXPLORER June 2020 data cut-off – 200mg population

Table 11. Data at each time point based on EXPLORER (June 2020 data cut-off, 200mg dose population), relying on “AVISIT” dimension.

Timepoint	Nr of patients
Baseline	16
Cycle 2 Day 1	15
Cycle 3 Day 1	14
Cycle 4 Day 1	13
Cycle 5 Day 1	13
Cycle 6 Day 1	11

Cycle 7 Day 1	11
Cycle 8 Day 1	6
Cycle 9 Day 1	7
Cycle 10 Day 1	5
Cycle 11 Day 1	8
Cycle 12 Day 1	8

b) Please clarify why HRQoL observations from EXPLORER were not combined with observations from PATHFINDER to increase the sample size.

HRQoL observations from EXPLORER were not combined with observations from PATHFINDER to maintain consistency across the key efficacy parameters used in the model (i.e. OS, PFS and TOT), all of which were derived from PATHFINDER (September 2022 data cut-off).

It was concluded that pooling EXPLORER and PATHFINDER 2022 data cut-offs were not necessary, given that:

1. The ITC for the main efficacy outcomes yielded statistically significant estimates, suggesting there was no requirement to augment the sample size.
    - Given the lack of necessity, the advantages increasing the sample size by including EXPLORER data were overshadowed by the introduction of additional heterogeneity, biases from differences in study design complicating the interpretation of treatment effects, heightened residual confounding bias in subsequent indirect comparisons, and, overall, increased analytical complexity required to address heterogeneity, biases, and other sources of variability.
2. European Medicines Agency issued a marketing authorisation based solely on the findings from PATHFINDER. This decision served as guidance for the subsequent development of the economic analysis.

B7. PRIORITY: Health-related quality of life data from PATHFINDER (Sept 2022 data cut, All AdvSM safety population, 200 mg avapritinib starting dose).

a) ***Please provide details on numbers of patients providing EORTC QLQ-C30 data at each time point (baseline, at end of Week 2, Week 4 and Week 8 and subsequently, every 8 weeks until cycle 17) to inform the mapped utility value associated with progression free (PF).***

Please see below the details on numbers of patients providing EORTC QLQ-C30 data at each time point. Using the dimension “AVISIT” or the dimension “ADY/7”.

PATHFINDER September 2022 data cut-off: avapritinib 200mg RAC-RE population, 1L

A total of 230 observations of 30 unique patients were used in the analysis. Table 12 (EORTC QLQ-C30 data) features the data at each time point to inform the mapped utility value associated with PF based on Pathfinder September 2022 data-cut (avapritinib 200 mg RAC-RE population, 1L, AdvSM), using the ‘AVISIT’ dimension:

Table 12. Data at each time point to inform the mapped utility value associated with PF, based on PATHFINDER (September 2022 data cut-off, 1L), relying on “AVISIT” dimension.

Timepoint	Nr of patients
Baseline	29
Cycle 1 Day 15	23
Cycle 2 Day 1	21
Cycle 3 Day 1	24
Cycle 5 Day 1	22
Cycle 7 Day 1	19
Cycle 9 Day 1	22
Cycle 11 Day 1	24
Cycle 14 Day 1	18
Cycle 17 Day 1	16

Abbreviations: Nr, number.

Table 13 shows the data collected at each time point (baseline, at end of week 2, week 4 and week 8 and subsequently, every 8 weeks until cycle 17) using the “ADY/7” field (round function used).

Table 13. Detailed breakdown of HRQoL at each time point using "ADY/7" field for 1L patients

Timepoint	Nr patients
Baseline	29
Week 2	23
Week 4	21
Week 8	21
Week 16	16
Week 24	12
Week 32	16
Week 40	17
Week 48	-
Week 56	-
Week 64	10

Abbreviations: Nr, number.

PATHFINDER September 2022 data cut-off: avapritinib 200mg RAC-RE population, 2L+

A total of 359 observations of 50 unique patients were used in the analysis. Note that for 1 observation the timepoint was blank; however, this observation was still included in the analysis because ADY was available, and it was before progression, using the 'AVISIT' dimension.

Table 14.Data at each time point to inform the mapped utility value associated with PF, based on PATHFINDER (September 2022 data cut-off, 2L+), relying on "AVISIT" dimension.

Timepoint	Nr of patients
Baseline	46
Cycle 1 Day 15	42
Cycle 2 Day 1	41
Cycle 3 Day 1	37
Cycle 5 Day 1	34
Cycle 7 Day 1	34
Cycle 9 Day 1	27
Cycle 11 Day 1	25
Cycle 14 Day 1	23
Cycle 17 Day 1	22

Abbreviations: Nr, number.

Table 15 below showcases this detail at each time point (baseline, at end of Week 2, Week 4 and Week 8 and subsequently, every 8 weeks until cycle 17) relying on the “ADY/7” field (round function used).

Table 15. Detailed breakdown of HRQoL at each time point using "ADY/7" field for 2L+ patients

Timepoint	Nr patients
Baseline	46
Week 2	42
Week 4	37
Week 8	30
Week 16	25
Week 24	25
Week 32	19
Week 40	20
Week 48	-
Week 56	1
Week 64	12

Abbreviations: Nr, number.

b) Please clarify whether missing EORTC QLQ-C30 data were imputed and, if appropriate, please provide details on the methods used.

Observations that had missing data in the EORTC QLQ-C30 domains were excluded from the analysis, given that the algorithm utilised to map EORTC-QLQ-C30 data to EQ-5D-3L (Young et al) could not be applied to derive the utility.

c) Please explain the implications of aggregating the HRQoL observations prior to progression into a single score for the utility value associated with PF.

The methodology used to estimate the utility value applied to the PFS involved several steps:

- Firstly, each observation with reported QLQ-C30 domains underwent mapping to an EQ-5D score and corresponding utility value based on UK tariffs.

- The utility values for each patient across all observations before progression were average, resulting in a single utility value associated with the pre-progression period for each patient.
- A grand mean of these utility values across all patients were calculated to derive a single utility value associated with the PFS state.

This approach of mapping utilities by using health dimension scores for each patient was deemed appropriate for several reasons:

i) It preserves individual variation in health dimension scores, capturing the diverse range of experiences and preferences within the population.

ii) The method enables the mapping algorithm to capture non-linear relationships between health dimensions scores and utilities at the individual level, providing a more accurate reflection of how changes in health dimensions may impact overall utility for each patient.

iii) By mapping utilities at the individual level, variations in preferences and responses to changes in health dimensions among different patients can be accounted for, allowing tailored estimates based on each patient' unique profile.

iv) This approach offers granularity in evaluating the effects on each patient's quality of life thereby facilitating further analyses regarding treatment efficacy.

v) The increased sensitivity to changes in health dimensions associated with individual-level mapping is expected to result in a more precise estimation of utility changes over time.

d) Please justify the choice of mapping algorithm by Young et al for mapping EORTC QLQ-C30 to EQ-5D.

As explained in CS Appendix P1.3, the selection of the algorithm from Young et al. was justified based on specific criteria. Firstly, the chosen algorithm needed to have publications reporting all necessary data for result replication. While the algorithms

from Proskorovsky et al. and Kharroubi et al. met inclusion criteria, they included elements specific to Multiple Myeloma (MM), limiting their applicability to datasets featuring only EORTC QLQ-C30 core questionnaire items, as seen in the AdvSM EORTC QLQ-C30 questionnaire.

Secondly, a comparison of the population used to estimate or validate algorithms was conducted concerning key aspects such as age, geographic area, disease type, and prognosis. The mean age of patients in selected algorithms aligned with AdvSM patients, except for data from Crott et al. and Versteegh et al., which included younger populations. Notably, Huan Xu et al. included patients with a considerably lower mean age.

The third consideration focused on the quality of life (QoL) in the datasets compared to QoL in the PATHFINDER trial. All included studies reported EORTC QLQ-C30 scores, with Young et al. and Kharroubi et al. showing the most similar QoL to PATHFINDER in terms of Average Global Health Score.

Lastly, the geography of tariffs used to estimate EQ-5D-associated utilities was considered, with Proskorovsky et al., Crott et al., and Young et al. utilizing the UK Tariff.

In conclusion, after evaluating these factors, the algorithm by Young et al. was deemed the most suitable for mapping EORTC QLQ-C30 to EQ-5D in AdvSM patients. Despite not being externally validated, its solid external validity was indicated by the associated shrinkage coefficient. The other two algorithms using the UK Tariffs had limitations, such as disease specificity and weak external validity, making them less suitable for AdvSM datasets.

B8. PRIORITY: Please provide a revised model that adjusts the PF and progressive disease (PD) utility values for ageing, in line with that done for the general population norms. Please clearly signpost the changes made to the model.

This has now been incorporated into the revised model. Updated base case results are presented in Appendix A.

B9. PRIORITY: Disutilities associated with adverse events.

a) Please clarify how the disutilities associated with adverse events were identified.

Table 16 lists the AEs used in the CEM and their associated disutilities The column on the right provides detailed information about how each disutility associated with each AE was informed.

Table 16. AE disutilities and sources

AE	Disutility	Detailed source
Thrombocytopenia	0.108	ID1374[19], Table 44
Anaemia	0.119	ID1374[19], Table 44
Febrile neutropenia	0.150	ID1374[19], Table 44
Neutropenia	0.090	ID1374[19], Table 44
Hypokalaemia	0.124	ID1374[19], Table 44
Neutrophil count decreased	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Platelet count decreased	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Blood alkaline phosphatase increased	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
White blood cell count decreased	0.100	ID1374[19], Table 44
Leucocytosis	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Hyponatraemia	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Hypophosphatemia	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Absolute lymphocyte decreased	0.100	ID1374[19], Table 44
AST increased	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Hyperglycaemia	0.072	Sullivan 2011[20], 064 - Other Hematologic Conditions
Acute myeloid leukaemia	0.175	Shabaruddin 2013[21], Secondary cancers (mean difference between utility value for AE and utility value for comparisons state)
Gastric haemorrhage	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Gastrointestinal haemorrhage	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Cardiac failure	0.063	Sullivan 2011[20], ICD9410 - Acute Myocardial Infarct
Colitis	0.047	ID1379[22], Table 39
Ascites	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Large intestine perforation	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Nausea	0.048	ID1374[19], Table 44
Vomiting	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Diarrhoea	0.048	ID1374[19], Table 44

AE	Disutility	Detailed source
Constipation	0.051	Sullivan 2011[20], 155 - Other Gastrointestinal Disorders
Gamma-glutamyl transferase increased	0.038	Sullivan 2011[20], 151 - Other Liver Diseases
Cholecystitis	0.058	Sullivan 2011[20], ICD9574 Cholelithiasis
Amylase increased	0.038	Sullivan 2011[20], 151 - Other Liver Diseases
Lipase increased	0.038	Sullivan 2011[20], 151 - Other Liver Diseases
ALT increased	0.038	Sullivan 2011[20], 151 - Other Liver Diseases
Total bilirubin increased	0.038	Sullivan 2011[20], 151 - Other Liver Diseases
Haemorrhage intracranial	0.117	Sullivan 2011[20], ICD9436 Cva
Encephalopathy	0.086	Sullivan 2011[20], ICD9348 Other Brain Conditions
Pneumonia	0.200	ID1374[19], Table 44
Pleural effusion	0.078	Sullivan 2011[20], ICD9518 Other Lung Diseases
Intervertebral disc protrusion	0.144	Sullivan 2011[20], ICD9722 Intervertebral Disc Disorder
Hypertension	0.038	Sullivan 2011[20], 098 - Essential Hypertension
Oedema peripheral	0.060	Shabaruddin 2013[21], Oedema (difference between mean utility value for adverse event and mean utility for comparison state)
Pyrexia	0.110	ID1379[22], Table 39
Intraductal proliferative breast lesion	0.003	Sullivan 2011[20], ICD9611 - Other Breast Disorders
Fatigue	0.073	ID1374[19], Table 44
Asthenia	0.115	ID1379[22], Table 39
Insomnia	0.066	Lubetkin 2018, Average of the values in Table 2
Dyspnoea	0.050	ID1379[22], Table 39
Cough	0.037	Sullivan 2011[20], ICD9519 Oth Respiratory System Diseases
Upper respiratory tract infection	0.037	Sullivan 2011[20], ICD9519 Oth Respiratory System Diseases
Sepsis	0.267	ID1374[19], Table 44
Hearth failure or shock	0.063	Sullivan 2011[20], ICD9410 Acute Myocardial Infarct
Headache	0.044	Sullivan 2011[20], ICD9346 Migraine
Sinusitis	0.002	Sullivan 2011[20], ICD9473 Chronic Sinusitis
Hypotension	0.057	ID1374[19], Table 44
Urinary tract infection	0.005	Sullivan 2011[20], ICD9599 Oth Urinary Tract Disorder
Erysipelas	0.195	ID1374[19], Table 44
Epistaxis	0.010	Sullivan 2011[20], 094 - Other Ear and Sense Organ Disorders

b) ***Please justify the assumption that disutilities for all adverse events included in the model last for 14 days, given the variation in length of duration for different events reported in Table 43 of CS.***

The model has now been revised using event durations for individual events as reported in Table 43 of CS. Updated base case results are presented in Appendix A.

c) ***Disutilities for adverse events associated with cladribine appear to be included in the model for patients assigned to a part of the avapritinib treatment arm in a PF state (Section B.3.6.4 of CS) for the comparison of avapritinib with 2L+ BAT only (see worksheet 'Engine AVA', column CZ of the model).***

   i. ***Please clarify whether these disutilities should also be assigned to patients PF and off treatment for the comparisons of avapritinib with 1L midostaurin and 2L+ cladribine. If so, please provide a revised model and clearly signpost the changes made to the model.***

Blueprint have reviewed the model, and IV disutility was not applied. AE disutilities were applied in off-treatment trace and have now been removed.

   ii. ***Please clarify whether these disutilities should also be assigned to patients treated with cladribine post-progression. If so, please provide a revised model and clearly signpost the changes made to the model.***

The model has now been updated to remove IV disutility in "off-treatment" trace. Updated base case results are presented in Appendix A.

Resource use and cost data

B10. PRIORITY: Sections B.3.6.4 and B.3.6.5 of CS suggest that subsequent treatment costs with cladribine are included in the model after treatment discontinuation and progression, respectively.

a) ***Please clarify whether subsequent treatment costs with cladribine are included in the model after discontinuation and progression, and***

whether costs of other subsequent treatment options should be considered. If so, please clarify how these have been included in the model and provide the justification for the approach and any assumptions made.

Clinical experts interviewed did not have experience with cladribine however the model has now been updated to allow easy usage of subsequent treatment cost.[15] Updated base case results are presented in Appendix A.

b) ***The model appears to track newly progressed patients in order to apply a one-off cost of cladribine for those post-progression. However, the implementation leads to the majority of cycles showing no progression. Please provide a revised model that incorporates the cost of post-progression treatment per cycle.***

The model has now been updated to include the implementation of subsequent treatments. Updated base case results are presented in Appendix A.

c) ***Please provide a revised model with sufficient flexibility to include or exclude subsequent treatment costs after discontinuation and progression. Please clearly signpost the changes made to the model.***

The model has now been updated and all changes have been signposted. Updated base case results are presented in Appendix A.

B11. Please clarify what percentage of patients in the NHS are prescribed the anti-sickness tablet of 8mg ondansetron OD for patients receiving midostaurin, and please clarify what percentage of other commonly prescribed anti-sickness tablets (e.g., domperidone and cyclizine) are used in the NHS for patients receiving midostaurin.

UK clinical experts agreed that ondansetron is prescribed as a default medication for those patients on midostaurin and would prescribe 8mg three times a day as needed.[15] One clinical expert mentioned prescribing enough for the initial month, while another suggested a potential duration of 1-2 months or 6 weeks. Although many patients take ondansetron, the clinical experts agreed that most patients do not require the full three times a day dosage and often retain the remaining medication at home for occasional use.[15]

It was noted, some patients may occasionally require more antiemetics or antidiarrheals, the prescription of alternative antiemetics like cyclizine is rare.[15] To reflect this, a scenario analysis is explored in the model, where 5% of patients receive cyclizine 50mg three times a day. Cyclizine has been included in the model to reflect this usage. Updated base case results are presented in Appendix A.

B12. Dose reduction and drug wastage.

a) ***How much drug wastage for avapritinib is expected due to patients switching from the 200 mg to 100 mg, 50 mg, or 25 mg dosing packages.***

UK clinical experts indicated that most patients would be prescribed a 28 supply initially and will be closely monitored. It was highlighted that individual cases vary and agreed there is likely little wastage, as in clinical practice patients will remain on the prescribed dose for at least 2-3 weeks before modifying the dose.[15] Clinical experts stated that they will have contact with the patients every 2-4 weeks in the first 3 months and highlight monthly supplies are prescribed to save the patients from burdensome trips to the pharmacy.[15] Both clinical experts agreed that once patients are stable, there is minimal wastage. It was estimated patients reach stability on their dose within 4-6 months and approximately 50% of patients would undergo dose reduction due to thrombocytopenia and platelet count.[15] The majority of these dose reductions are to 100mg. This has been updated and included as a scenario in the model.[15]

b) ***Please provide a revised model with sufficient flexibility to include or exclude drug wastage for avapritinib. Please signpost the changes made to the model.***

Functionality has been included in the model and changes have been signposted.

B13. Please clarify the source for the relative dose intensity reduction of 90% used in the model for midostaurin.

Feedback from clinical experts in the UK indicates that among patients initiating midostaurin at 100mg, 50% experience a dose reduction to 50mg. Furthermore, among this subgroup of patients with a 50mg reduction, approximately 30% can

titrate back up to the 100mg dose. Resulting in a dose intensity reduction of 90% (1-(0.5-0.3)*0.5)=0.9).[23]

Electronic model corrections

B14. **PRIORITY: Please provide a revised version of the model where changes made to the active comparison allow the base-case settings to be set to default values for each comparison.**

A “reset to default settings” macro has been implemented next to the comparator selection which resets all settings to the base case values.

B15. Please correct the inconsistencies in the number of probabilistic simulations used to compute total costs and total QALYs for avapritinib and comparator in rows 5-7 of worksheet ‘PSA_data’, where some of the computations are based on 5,000 simulations and others 10,000 simulations. Without this change, the probabilistic mean cost-effectiveness results are significantly different from the deterministic results.

Updated base case results are presented in Appendix A.

B16. Please correct cell D13 on worksheet ‘QoL Data’, which is not referring to the correct PF utility for the comparison avapritinib with cladribine.

Cell D13 has been corrected so that the cladribine comparison is using the correct “Pathfinder 2L+” utility value.

B17. Please correct cell C37 on worksheet ‘QoL Data’, which is always set to zero even when the disutility for treatment administration is set to ‘Included’.

The model has been updated. Cladribine IV disutility has been implemented in cell E42 on the HRQoL sheet. The QALY traces in “Engine QALY” and “Engine Comp” includes a conditional for the disutility to only be applied to cladribine.

B18. Please correct the references in column K on worksheet 'Engine COMP' for probability of death pre-transplant, which is referring to the incorrect survival curve.

The survival curves used are the OS curves for the respective treatment. Blueprint believes the pre-transplant survival curve is referring to the correct survival curve as it uses the comparator OS curve.

B19. PRIORITY: Please correct cell D13 on worksheet 'QoL Data', which selects the progression-free utility value of 1L setting for 2L+ cladribine setting.

This has been corrected (addressed in a previous question).

Section C: Textual clarification and additional points

C1. PRIORITY: Please provide a breakdown of the specific patients included in the following Figures/Tables, as there is either a discrepancy in the reporting, or it is not clear which population is reported:

a) Table 10

Patients from PATHFINDER (September 2022 data cut-off) with a starting dose of 200 mg avapritinib daily. Table 10 in the Company Submission reports on both the RAC-RE population and the safety population, as indicated in the header row. Please see Table 17 below for an overview.

Table 17. Overview of patient populations reported in Table 10 of the CS

Study	Data cut	Population name as per table	n	Line of therapy	Analysis group	AdvSM subtype	Intervention	Source of data
PATHFINDER	September 2022	Safety population 2L+	67	2L+	Safety population	All AdvSM	200 mg avapritinib starting dose	Blueprint Medicines. PATHFINDER Clinical summary (2022 data cut-off)
		Safety population 1L	38	1L				
		Safety population all	105	1L+				
		RAC-RE population 2L+	51	2L+	RAC-RE Population			
		RAC-RE population 1L	30	1L				
		RAC-RE population all	81	1L+				

b) Table 13

Patients from the safety population of PATHFINDER (September 2022 data cut-off) with a starting dose of 200 mg avapritinib daily. Please see Table 18 below for an overview.

Table 18. Overview of patient populations reported in Table 13 of the CS

Study	Data cut	Population name as per table	n	Line of therapy	Analysis group	AdvSM subtype	Intervention	Source of data
PATHFINDER	September 2022	ASM	20	1L+	Safety population	ASM	200 mg avapritinib starting dose	Blueprint Medicines. PATHFINDER Clinical summary (2022 data cut-off)
		SM-AHN	68	1L+		SM-AHN		
		MCL	15	1L+		MCL		
		2L+	67	2L+		All AdvSM		
		1L	38	1L		All AdvSM		
		All AdvSM	105	1L+		All AdvSM		

c) Table 17

- Clinical trial data (avapritinib cohort):[24]
    - Data from patients treated with avapritinib in the safety populations of the EXPLORER and PATHFINDER trials was used (both April 2021 data cut-off)
- Real-world data (midostaurin and cladribine cohorts):[24]
    - A global, observational, retrospective chart review study was conducted at 6 study sites (4 European, 2 US) to identify and collect data from AdvSM patients who received treatment with midostaurin or cladribine

- De-identified data from eligible patients were abstracted from medical records into a standardised electronic case report form from March 26, 2021 to October 4, 2021

Please see Table 19 below for an overview.

Table 19. Overview of patient populations reported in Table 17 of the CS

Study	Data cut	Population name as per table	n	Line of therapy	Analysis group	AdvSM subtype	Intervention	Source of data
Pooled EXPLORER and PATHFINDER	April 2021	Avapritinib cohort	176	1L+	Safety populations of EXPLORER and PATHFINDER	All AdvSM	Avapritinib (all examined starting doses)	Reiter 2022
Real-world data	N/A	Midostaurin cohort	94	1L+	N/A		Midostaurin	
Real-world data	N/A	Cladribine cohort	44	1L+	N/A		Cladribine	

d) Figure 24-25

Figures 24 and 25 are sourced from Pilkington et al. (2022). These figures show data from the following populations, with the specific populations used for each analyses indicated in the figure:[14]

- Avapritinib population
  - the PATHFINDER RAC-RE population (April 2021 data cut-off)
  - the pooled EXPLORER and PATHFINDER RAC-RE population (April 2021 data cut-offs), full population

- those who received prior therapy in the pooled EXPLORER and PATHFINDER RAC-RE populations (April 2021 data cut-offs)
- those who were midostaurin-naïve in the pooled EXPLORER and PATHFINDER RAC-RE populations (April 2021 data cut-offs)
- those who received 200 mg avapritinib starting dose those who received prior therapy in the pooled EXPLORER and PATHFINDER RAC-RE populations (April 2021 data cut-offs)

- Midostaurin population
  - Primary efficacy population from the D2201 clinical trial

Please see Table 20 below for an overview.

Table 20. Overview of patient populations reported in Figure 24 and Figure 25 of the CS

Study	Data cut	Population name as per table	n	Line of therapy	Analysis group	AdvSM subtype	Intervention	Source of data
Pooled EXPLORER and PATHFINDER	April 2021	Avapritinib population: Pooled (RACE-RE, n = 79)	79	1L+	RAC-RE	All AdvSM	Avapritinib (all examined starting doses)	Pilkington 2022
PATHFINDER	April 2021	Avapritinib population: PATHFINDER (RACE-RE, n = 31)	31	1L+				
Pooled EXPLORER and PATHFINDER	April 2021	Avapritinib population: Pooled (RAC-	53	2L+				

		RE, prior therapy, n = 53)						
Pooled EXPLORER and PATHFINDER	April 2021	Avapritinib population: Pooled (RAC-RE mido-naïve, prior therapy, n = 46)	46	1L+ and midostaurin-naïve				
Pooled EXPLORER and PATHFINDER	April 2021	Avapritinib population: Pooled (RAC-RE 200 mg, n = 42)	42	1L+			200 mg avapritinib starting dose	
Study D2201	Final	D2201 (PEP, n = 89)	89	?	PEP		Midostaurin	

e) Table 21

Data from the PATHFINDER (September 2022 data cut-off) were used. The following populations were used (as indicated in the table):

- Avapritinib 1L: Patients who received 200 mg avapritinib first-line in PATHFINDER (2022 data cut-off). Analyses are shown with those in the RAC-RE population and those in the safety population, as indicated in the table rows.
- Avapritinib 2L+: Patients who received 200 mg avapritinib second-line or later in PATHFINDER (2022 data cut-off). Analyses are shown with those in the RAC-RE population and those in the safety population, as indicated in the table rows.
- Midostaurin 1L: Patients who received first-line midostaurin in a retrospective chart review study[1,25] that collected longitudinal, individual-level data via medical chart abstraction on patients treated at centres of excellence in the UK, US, Austria, Spain, and Germany.

- Cladribine 2L+: Patients who received 2L+ cladribine in a retrospective chart review study[1,26] that collected longitudinal, individual-level data via medical chart abstraction on patients treated at centres of excellence in the UK, US, Austria, Spain, and Germany.
- BAT 2L+: Patients who received 2L+ best available treatment in a retrospective chart review study[1,27] that collected longitudinal, individual-level data via medical chart abstraction on patients treated at centres of excellence in the UK, US, Austria, Spain, and Germany.

Please see Table 21 below for an overview.

Table 21. Overview of patient populations reported in Table 21 of the CS

Study	Data cut	Population name as per table	n	Line of therapy	Analysis group	AdvSM subtype	Intervention	Source of data
PATHFINDER	September 2022	Avapritinib 1L (200 mg PATHFINDER RAC-RE population)	30	1L	RAC-RE	All AdvSM	200 mg avapritinib starting dose	Data on file, ECS analysis 1L mido
PATHFINDER	September 2022	Avapritinib 1L (200 mg PATHFINDER Safety population)	38	1L	Safety			
PATHFINDER	September 2022	Avapritinib 2L+ (200 mg PATHFINDER RAC-RE population)	51	2L+	RAC-RE			Data on file, ECS analysis 2L+ cladribine or 2L+ BAT
PATHFINDER	September 2022	Avapritinib 2L+ (200 mg PATHFINDER safety population)	67	2L+	Safety			
Real-world data	N/A	Mido-1L	58	1L	N/A		Midostaurin	Data on file, ECS analysis 1L midostaurin
Real-world data	N/A	Clad- 2L+	24	2L+	N/A		Cladribine	Data on file, ECS analysis 2L+ cladribine
Real-world data	N/A	BAT- 2L+	67	2L+	N/A		Best available therapy	Data on file, ECS analysis 2L+ BAT

C2. PRIORITY: In Table 2, it states "Avapritinib received EU marketing authorisation in March 2022 as a monotherapy for the treatment of adult patients with ASM, SM-AHN, and MCL, after at least one systemic therapy". Please clarify whether avapritinib received EU marketing authorisation at second line for all subtypes of AdvSM, or whether the restriction 'after at least one systemic therapy' only relates to MCL.

The restriction 'after at least one systemic therapy' applies to all subtypes of AdvSM.

C3. Please provide the footnote for the * in Table 8 ('Prior systemic therapy' row)

The footnote should read as 'prior therapies are coded using WHO DD B2 enhanced, version March 2017.'[2]

C4. Please check and clarify wording the second paragraph on page 66, regarding the PFS KM curves presented for the PATHFINDER population, as it does not make sense.

The paragraph has been rephrased below:

PFS Kaplan-Meier (KM) curves are presented for individual disease subtypes in Figure 10, and by prior systemic therapy in Figure 11. As of the data cut-off, the median PFS was not met in patients who had received prior systemic therapy (i.e. 2L+ patients) and was 39.4 months (95% CI: 39.4, not evaluable [NE]) in patients who had not received prior systemic therapy (i.e. 1L patients).

C5. Please provide the footnote for the [2] in Table 21, Page 96

The footnote should read:

Stabilised weights were generated using the following baseline characteristics: age, sex, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16 ×

10^9/L or higher, serum tryptase concentration of 125 ng/mL or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel, number of prior lines of therapy, prior use of tyrosine kinase inhibitor therapy, biologics, and cytotoxic therapy. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

Please note that this footnote should also be added to the IPTW column in Figure 20 of the company submission (page 93).

C6. PRIORITY: Please confirm the number of patients who achieved a CR or CRh in PATHFINDER who had previously received one or more prior systemic therapies, as the percentage (20%) and sample sizes (5/51) do not correspond (first paragraph, page 110).

The total number of patients who achieved CR or CRh was reported in error. To clarify, of the 51 patients who had previously received prior systemic therapy and who received 200 mg avapritinib starting dose, 10 patients (19.6%) achieved a CR or CRh.[2]

C7. PRIORITY: Please check the final paragraph on page 111, as there appears to be an error: "Notably, in the pivotal PATHFINDER trial, patients demonstrated improvements in all domains of both assessment tools". This is inconsistent with Table 15 which demonstrates a decline in EORTC QLQ-C30 cognitive functioning domain from baseline to Cycle 17.

We agree this is an error and should be corrected to 'notably, in the pivotal PATHFINDER trial, patients demonstrated improvements from baseline in AdvSM-SAF TSS and EORTC QLQ-C30 global health status score, with improvements observed across all domains of the EORTC QLQ-C30 except cognitive functioning.'

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Appendix A – Revised cost-effectiveness base case results

Executive summary

Blueprint Medicines have additionally submitted an updated PAS Evidence Submission template that reflects these changes with a full Excel model. Blueprint Medicines are providing an update to cost-effectiveness model base case results (CS section B3.11), in line with requests outlined by EAG.

In response to EAG clarification question B3, the revised base case and scenario analyses using the latest data cut will be provided at a later date.

Cost-effectiveness results

Deterministic base case results

Table 22. Discounted base case cost-effectiveness results at PAS price

Technology	Total costs (£)	Tota LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	6.11	4.31	[redacted]	2.86	2.27	[redacted]	[redacted]
Midostaurin	[redacted]	3.24	2.03					
Comparison B: Avapritinib vs BAT (as proxy for cladribine), 2L+								
Avapritinib	[redacted]	4.85	2.90	[redacted]	1.78	1.33	[redacted]	[redacted]
BAT	[redacted]	3.07	1.58					
Comparison C: Avapritinib vs cladribine, 2L+								
Avapritinib	[redacted]	4.04	2.50	[redacted]	1.29	1.09	[redacted]	[redacted]
Cladribine	[redacted]	2.75	1.41					

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, Patient access scheme.

Table 23. Discounted base case NHB and NMB results at PAS price

Technology	Total costs (£)	Tota QALYs	Incremental costs (£)	Incremental QALYs	NHB (WTP £36,000)	NHB (WTP £30,000)	NMB (WTP £36,000)	NMB (WTP £30,000)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	4.31	[redacted]	2.27	11.14	12.84	[redacted]	[redacted]
Midostaurin	[redacted]	2.03						
Comparison B: Avapritinib vs BAT (as proxy for cladribine), 2L+								
Avapritinib	[redacted]	2.90	[redacted]	1.33	-1.04	-1.56	[redacted]	[redacted]
BAT	[redacted]	1.58						
Comparison C: Avapritinib vs cladribine, 2L+								

Technology	Total costs (£)	Tota QALYs	Incremental costs (£)	Incremental QALYs	NHB (WTP £36,000)	NHB (WTP £30,000)	NMB (WTP £36,000)	NMB (WTP £30,000)
Avapritinib	[redacted]	2.50	[redacted]	1.09	-1.29	-1.79	[redacted]	[redacted]
Cladribine	[redacted]	1.41						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; NMB, Net monetary benefit

Sensitivity analysis

Comparison A: 1L avapritinib versus midostaurin

Table 24: Probabilistic sensitivity analysis results for 1L avapritinib versus midostaurin

	Cost (£)			QALYs			ICER (£/QALY)
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	
Base case	[redacted]	[redacted]	[redacted]	4.31	2.03	2.27	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	4.15	1.99	2.16	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	3.57	1.73	1.73	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	4.63	2.24	2.51	[redacted]

Figure 9. Cost-effectiveness plane and cost-effectiveness acceptability curve for 1L avapritinib versus midostaurin

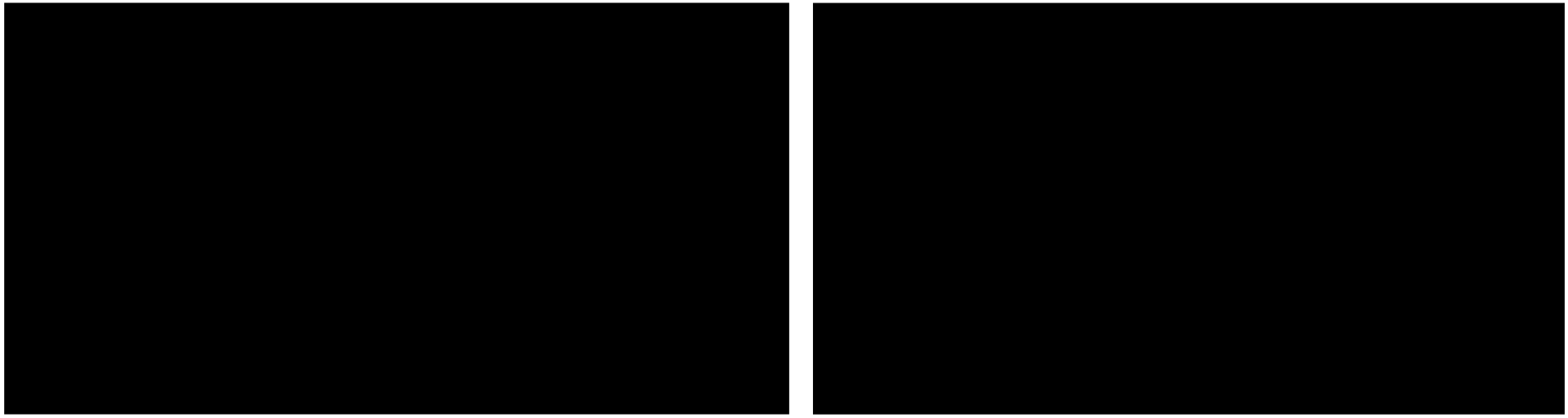

Figure 10. Tornado diagram for OWSA for 1L avapritinib versus midostaurin

Comparison B: 2L+ avapritinib versus BAT (as proxy for cladribine)

Table 25: Probabilistic sensitivity analysis results for 2L+ avapritinib versus BAT (as proxy for cladribine)

	Cost (£)			QALYs			ICER (£/QALY)
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	
Base case	[redacted]	[redacted]	[redacted]	2.90	1.58	1.33	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	0.29	0.16	1.31	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	2.59	1.33	1.09	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	3.16	1.80	1.51	[redacted]

Figure 11: Cost-effectiveness plane and cost-effectiveness acceptability curve for 2L+ avapritinib versus BAT (as proxy for cladribine)

Figure 12: Tornado diagram for OWSA for 2L+ avapritinib versus BAT (as proxy for cladribine)

Comparison C: 2L+ avapritinib versus cladribine

Table 26: Probabilistic sensitivity analysis results for 2L+ avapritinib versus cladribine

	Cost (£)			QALYs			ICER (£/QALY)
	Avapritinib	Comparator	Incremental	Avapritinib	Comparator	Incremental	
Base case	[redacted]	[redacted]	[redacted]	2.50	1.41	1.09	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	2.48	1.42	1.07	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	2.23	1.20	0.85	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	2.72	1.63	1.27	[redacted]

Figure 13: Cost-effectiveness plane and cost-effectiveness acceptability curve for 2L+ avapritinib versus cladribine

[redacted]

Figure 14: Tornado diagram for OWSA for 2L+ avapritinib versus cladribine

Scenario analysis

Further scenario analyses are presented to reflect consistent modelling approaches as suggested by the EAG during the EAG clarification meeting on the 7th of March 2023. Consequently, Blueprint has updated only the most influential scenarios, as discussed during EAG clarification meeting. However, all scenarios in CS remain relevant, although updating results was not feasible at this time.

Table 27:Comparison A: Scenario analysis versus midostaurin 1L

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
Base case			[redacted]	[redacted]
Scenario 1: DoT using trial data (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program)	DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]
Scenario 2: DoT as proxy for avapritinib PFS (RWE CUP - median DoT of 17 months)	Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS	[redacted]	[redacted]
Scenario 3: DoT as proxy for avapritinib PFS (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program) Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS using DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]

Table 28: Comparison B: Scenario analysis versus BAT 2L+ (as proxy for cladribine)

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
Base case			[redacted]	[redacted]
Scenario 1: DoT using trial data (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program)	DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]
Scenario 2: DoT as proxy for avapritinib PFS (RWE CUP - median DoT of 17 months)	Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS	[redacted]	[redacted]
Scenario 3: DoT as proxy for avapritinib PFS (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program) Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS using DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]

Table 29: Comparison C: Scenario analysis versus cladribine 2L+

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
Base case			[redacted]	[redacted]
Scenario 1: DoT using trial data (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program)	DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]
Scenario 2: DoT as proxy for avapritinib PFS (RWE CUP - median DoT of 17 months)	Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS	[redacted]	[redacted]
Scenario 3: DoT as proxy for avapritinib PFS (PATHFINDER 2022 data cut-off adjusted by ECS - median DoT of 42 months)	DoT from real world evidence (compassionate use program) Avapritinib PFS from Pathfinder RAC-RE data analysis (data-cut 2022)	Using avapritinib DoT as proxy for PFS using DoT from Pathfinder ECS adjusted data analysis (data-cut 2022)	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted] **(UK Masto),** [redacted] **(Leukaemia Care)**
2. Name of organisation	The UK Mastocytosis Support Group and Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**The UK Mastocytosis Support Group** is a small national charity that promotes the well-being of people with mastocytosis and other mast cell diseases (MCDs). We educate people with MCDs, their families, and medical professionals by sharing best practices in medical and self-care; promote access to knowledgeable care and access to medications; and catalyse research. Funding comes from fundraising activities, events, grants and subscriptions, and from pharmaceutical companies. We have regular contact with several thousand people with a range of mast cell diseases. **Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, accounting for 18.82% of Leukaemia Care's annual income in 2022.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**UK Masto:** Blueprint Medicines: Honorarium for 1 trustee and 1 volunteer to participate in the steering committee meeting for design of a survey on quality of life in mastocytosis patients, and then for discussion of data and publications plans: £1350 Expenses paid for travel for trustee/patient to speak to European staff about life with mastocytosis: £430 Honorarium for trustee to participate in meeting of European leaders of patient groups: £294 **Leukaemia Care**: Bristol Myers Squibb - £30,000* (£15,000 core funding and *£15,000 on behalf of the Blood Cancer Alliance, of which Leukaemia Care is a member.

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?	Anonymous survey of patients in the UK and Europe carried out from December 2022 to April 2023 (PRISM Study). UK Masto survey of UK patients and carers in December/January 2023/4. (Respondents were given the options of providing an email address for recontact.)

NICE National Institute for Health and Care Excellence

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Symptoms** in advanced mastocytosis include those **caused by the release of mast cell mediators** including anaphylaxis (54% of respondents in the recent UK Masto survey), cramping and diarrhoea (54%), upper GI pain due to hyperacidity (54%), skin rash/hiving/itching (45%), bone pain (36%), vomiting, (27%), low mood (27%). Patients also react to triggers in the normal environment (airborne cleaning chemicals, perfumes, foods, ingestion of alcohol, exposure to heat or cold or extreme temperature changes, friction on the skin, vibration, some medicines and anaesthetics) that can lead to mild reactions or anaphylaxis. Mastocytosis may also cause osteoporosis, including in men and at younger ages. In addition, people with advanced mastocytosis may have **symptoms related to the organomegaly (liver and spleen) and effects on bone marrow** of having significant proliferation of mast cells that lead to fatigue (54%), difficulty concentrating (27%), localised and generalised pain (e.g. from organomegaly), and susceptibility to infection. In addition, patients deal with the **emotional effects of having a rare disease with a shortened life expectancy**. (Median overall survival of 5.7 years (95% CI 0.6–4.5) for patients with aggressive systemic mastocytosis, 1.9 years (0.0–5.2) for those with mast cell leukaemia, and 2.9 years (2.5–3.3) for individuals with systemic mastocytosis with an associated haematological neoplasm. (Sperr WR et al. Lancet Haematol. 2019 Dec;6(12):e638-e649.)) **Patient views:** -- “There were a large number of **foods and drinks which I could not tolerate** [before joining the Avapritinib trial]. I was also extremely easily **fatigued** by physical exercise and tasks. I felt **unable to stay away from home** for even a short period because of the **unpredictability of my digestive system**. (SM-AHN patient)” --“I suffered episodes, lasting about an hour, of **excruciating abdominal pain with diarrhoea and vomiting** at least once, sometimes two or three times every 24 hours, usually without a trigger. Nausea and vomiting in response to very small amounts of alcohol and caffeine. Also extensive and intense urticaria pigmentosa. My tryptase was always extremely high, on one occasion it was reported to be immeasurable at over 2,000. (ASM patient)” --“It has affected my ability to live. Being **sensitive to extreme temperatures** limits my activities, and my symptoms often cause me to miss work or social activities. We no longer eat out often, and I have to take precautions for symptoms whenever I leave the house. (ASM patient)”

	--“This disease (pre-midostaurin) was extremely hard to live with. It caused me to stop working at 60 due to **pain, fatigue, itching and severe stomach problems**, which could not be alleviated by non-TKI drugs. Since TKI, my life has improved, enabling me to do some part time work. However, there is still much I cannot do due to bone pain (constant); dizziness; post drug nausea, and ongoing dragging fatigue. (ASM patient)” --“I have seen therapists, take antidepressants, have seen dietician related to side effects of midostaurin, and consulted a financial advisor. As the disease progressed, when I was SSM I developed **chronic and uncontrollable explosive diarrhoea**…every bowel movement, and limited some of my social interactions

	dependent on access to a restroom. Travel was difficult, and I sometimes didn't make it to a bathroom. Carried wipes and change of clothes. (ASM patient)" --"Initially an **enlarged spleen** was my problem. **Itching** was a severe problem at beginning. **Tiredness and lack of energy** also… The consequent **osteoporosis** has been one of the major problems as I have broken four bones in the space of twelve years. This has affected my confidence greatly. My recent diagnosis of Leukaemia was made after a routine blood test and has been a great blow. (SM-AHN patient)" --"In the early years my **fatigue, pain and regular reactions** (especially to stress and fatigue, a vicious cycle) caused me to be unable to work. This in turn has a negative impact upon mental health and I have battled with **depression and anxiety**... I was fortunate to be granted **early retirement on medical grounds** and along with benefits. One of my biggest expenses is taxis as we don't drive. We used to walk a lot but now I cannot. My **husband was also given early retirement** to be at home with me as I was very poorly in the early days... I don't manage much of a social life and now rarely receive invitations to events that people assume I won't attend. (SM-AHN patient)" --" I have given up voluntary work as I have become very unreliable - frequently I cannot keep to my commitments because I am **too tired or because of digestive problems**. I have had to give up playing in the local orchestra as I have missed too many rehearsals and keep letting them down. I miss making music. I struggle to be active with my grandchildren. My husband has become my carer when I am unwell and worries about me. If I want to go out in the evening I make sure I have a quiet afternoon. I have to eat small amounts often and I eat very slowly so we rarely go out for a meal at a restaurant. (ASM patient)" --"The treatment has taken over our life. Everything we now do revolves around this disease in one way or another. Due to the ongoing disease burden, we have had to change everything we do, from what time we can go out in the morning (due to having to wait for my **post midostaurin nausea** to pass), to our holiday destinations (no flights over 3 hours due to **pain and fatigue**), length of holidays (5 days max, or I will be in bed with exhaustion for one to two weeks afterwards). We have had to shift our main meal to lunch time to avoid **nighttime GI problems**, and our usable day has shrunk to about 6 hours. My wife has had to take onboard most of the housework due to my **fatigue, pain, dizziness**... and due to not working we have had to terminate our cleaners. The strain on her has been, and will continue to be huge, and unfair. This disease causes a complete rethink of life and takes away all vestiges of 'life as you knew it'. (ASM patient)" --"Severe **intolerance to a variety of foods and drinks**, difficult to identify some of the not tolerated foods. Dramatic **loss of weight. Loss of sleep**. Unable to plan social events. Having to avoid the slightest trace of alcohol in foods, as flavouring for example. Eating non tolerated food resulted in **severe stomach pain, vomiting and diarrhoea**." **Effect on Carers:**

	--“My husband had to miss work for some trips to my doctor that was 4 hours away, or local tests requiring sedation. He had to drive me to appointments for a drug trial at a different city. Being in a drug trial itself was stressful but adding driving sometimes 5 hours was very stressful for us both, especially because of my uncontrollable diarrhoea and we could not take the train as this was during covid pandemic. Because of my prognosis, I know he is worried but does not express this.” **Carers’ views:** --“He [the patient] used to have his own manufacturing business but has not been able to do that for a long time and now works in the motor trade at a desk job. He used to be very active and participated in sports. He had a prodigious memory and never forgot anything. ASM meant that my partner had serious reactions to many foods and drinks and sometimes to things unknown, and often ended up in hospital. It has affected my partner’s quality of life- he is no longer able to participate in sports, and he gets very tired. He had a lot of pain with the ASM - in his joints, his back, his stomach, headaches… He is no longer able to play games with our youngest son. His tiredness has impacted our married lives as he falls asleep early at night leaving me to find ways to occupy my time alone. Our friends do not understand the disease or its impact and think we invent the tiredness and inability for him to participate in sport.” -- NHS initially diagnosed him with mast cell leukaemia and gave him six months to live. They informed him of this in letter which I think is appalling. The 2nd opinion provided months later by Guys hospital was ASM. Treatment was started almost year after diagnosis and in this time he was losing weight at around 200g a day. For months I expected to find him dead in the house. I was unable to leave him and I believe it traumatised our son.

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7. What do patients or carers think of current treatments and care available on the NHS?	The primary drug on offer is midostaurin (one comment on interferon below). No comments on cladribine or imatinib though small numbers had tried them in the past. None were on them or interferon now. --"I took [medical leave from work] while working for various doctor appointments and on days side effects of **interferon** were bad. I was retired by the time I was on **midostaurin**, but would not have been able to continue working as I had severe nausea and/or vomiting every morning." --"In my case, **[midostaurin caused] projectile vomiting and nausea**. The **positive effects did not last as long and were not as deep as they are on avapritinib**. The advantage for me was it helped until I was able to get into the avapritinib drug trial. I have the same concern about unknowns of long-term effects of drug on body [as I do about avapritinib]. …I stayed on midostaurin for a year, trying everything to conquer nausea and vomiting, but never did. It also started being ineffective for me". -- "*Advantages*: Midostaurin enabled me to reclaim some useful hours each day when I can live again (albeit with significant limits), but most significantly, it **stops the nightmare itching**, and **dramatically reduces GI problems and anaphylaxis**, enabling some semblance of life to resume. *Disadvantages* include **nausea** after taking the TKI, even with 8mg Ondansetron. It **doesn't stop the bone pain, or significantly reduce the fatigue symptoms**. Also, some **residual GI problems** remain, although significantly reduced. Also some **dizziness remains**, but to date, zero anaphylaxis." --"Midostaurin has **largely eradicated my symptoms** and allows me to live normally. The only side effects I have encountered are **nausea and vomiting** approximately 1 hour after taking a dose." -- "Midostaurin **worked well for a while for me,** shown by a big decrease in my tryptase level, and my rash disappeared. My **improvements plateaued and my tryptase started to increase**; My symptoms were starting to return and I was suffering **intolerable nausea with vomiting** despite anti-nausea medications. It was decided that it was advisable to stop." --"She finds it rather **unpalatable**! 4 large oily capsules twice daily. It would be good if there could be a more concentrated dose and therefore only one to take at a time."

8. Is there an unmet need for patients with this condition?	While patients who have had access to midostaurin are grateful it is available and funded, it is not curative, some patients find it stops working as well as it first did after some time, and it causes significant GI symptoms in many patients. (Vomiting is very common). Patients with advanced mastocytosis need medications that are easily tolerated and more effective at preventing symptoms and prolonging life. In the PRISM survey of UK patients with advanced SM, the mean satisfaction with their treatment was 2.26 on a scale of 1-7. Evidence from the avapritinib trials (Pathfinder and Explorer), as well as real world data from the UK from patients receiving it via compassionate use, shows that avapritinib has better outcomes than the other medications currently available in the UK in both a trial setting (Reiter A et al Leukemia. 2022; 36:2108-2020. Pilkington H, et al Future Oncol. 2022 Apr;18(13):1583-1594.) and as used in a UK clinic (Saunders et al, 2022. "The use of Avapritinib in Advanced Systemic Mastocytosis: Report of An Open-Label Compassionate Use Program in the United Kingdom", poster presented at the meeting of the American Hematology Society meeting December 2022.) Patients are not being adequately treated and there is a medication available which has shown to have superior outcomes while being better tolerated.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients describe improvements in their symptoms, including in their general ability to get on with normal life. --"Had I not been accepted on the avapritinib trial I would eventually become unable to care for our home and garden, but as it is I am continuing to do so in partnership with my husband. I am also able to care for my grandchildren, carry out some voluntary work and have a social life with my family and friends. I put any unusual weariness down to my age rather than to my health. (SM-AHN patient)" --"It has been amazing. Although I am no longer professionally active, I believe that the medication makes me a more useful member of society. (SM-AHN patient)" --"Our biggest help now has been the treatment. Avapritinib has made an enormous difference to us. I do actually wonder if, had this been available when I was younger, I may have been able to continue working and making my contribution in society. In two years I have only had two of my bigger reactions, and these were much milder than previously. I am getting far less of the overwhelming fatigue episodes and can manage more walks than I did. Not a lot by other people's standards, but enough to be allowing some enjoyment when we are away from home. My UP rash has disappeared completely and my skin doesn't react to the things it did. I don't hive at friction or heat and I now can have a normal hot shower or bath. This may not sound like much but it is enormous for me. I SLEEP properly most nights. Feeling better regarding the Mastocytosis is helping me in coping with my other conditions as I am feeling mentally stronger. (SM-AHN patient)" -- "It dropped my bone marrow infiltration from 70% to 3%, and my tryptase from 690 to 25. It eliminated my cutaneous mastocytosis spots, stopped my flushing, resolved diarrhoea problems and I now have no spleen pain. For me, the advantage of this drug was the side effects had less impact, and the results were faster and lasted longer." (ASM patient who has taken midostaurin and is now on avapritinib) --"Better health generally and stability - it is wonderful to be able to leave home with so much more confidence. I have stayed out of A&E so I am not tying up precious paramedics and beds. I can even have a small amount of alcohol if I want it. I even don't have the self-consciousness of the UP rash or the flushing. I have had none of the episodes of pain and diarrhoea that were so embarrassing when it happened away from home. I can take longer walks as I have a bit more energy and I sleep so much better now as I don't itch and flush through the night. I also am not getting the mediator effect of feeling wide awake when waking up just minutes after falling asleep and then being awake for hours".

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	--"The only side effect which I find unpleasant at times is watering and puffy eyes. I also occasionally feel a bit vague but it soon passes and has not had any adverse effects on my life so far." --"The unknown long-term impact and lack of carcinogenic studies. The studies with GIST where some patients developed other gene mutations and resulting medical condition. However for those with advanced forms of masto, I think these risks are acceptable trade off." --"Puffy face. A slight increase in the bruising I already get because of being on anticoagulants."

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.	Avapritinib use is limited to those with platelet levels that are over 50x10(9)L because of an increased risk of brain bleed in those with low platelets. A 2021 study (DeAngelo DJ, et al. Nat Med. 2021;27(12):2183-2191*)* found that patients given avapritinib as first line treatment had better outcomes than those using it as second line to midostaurin, so it would be beneficial to have it available as line agnostic. Patients receiving it as second line also had a good response and should not be excluded. Avapritinib has shown good efficacy in all types of advanced systemic mastocytosis.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We do not know of any specific equality related concerns that should be considered in regard to avapritinib.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Advanced systemic mastocytosis significantly shortens life expectancy. It also causes considerable disability. In addition to experiencing the symptoms that are common to advanced haematologic diseases, such as extreme fatigue, anaemia, lymphadenopathy and organomegaly they also have the symptoms of ongoing mast cell degranulation such as cramping, diarrhoea, vomiting, and sensitivity to environmental pollutants. Some also experience unpredictable anaphylaxis to known and unknown triggers. • There is considerable unmet need in advanced systemic mastocytosis because current treatments are not curative, do not manage all symptoms, and can cause significant side effects. Trial and real-world data show responses in avapritinib are quicker and deeper than in midostaurin (the primary comparator), and it is generally well tolerated (with side effects being reversible with lower doses where needed). • Patients who have had access to avapritinib report improved quality of life with minimal side effects. • Advanced SM patients who have had both avapritinib and midostaurin prefer avapritinib because it does not cause vomiting, because quality of life improves on it, and because the positive effects have been durable. • Patients with all types of advanced mastocytosis should be eligible for avapritinib treatment at whichever point in the treatment pathway their haematologists believe it is most appropriate given evidence of efficacy in all types and at all points.

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Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on 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.

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 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	[redacted], nominated by British Society of Allergy and Clinical Immunology
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	National Health Service
5b. 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
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent disease progression, improve morbidity, increase overall survival and improve quality of life,
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in mast cell burden (bone marrow, skin and viscera, serum tryptase, variant allele burden) organ dysfunction (including liver, bowel and skin) improved overall disease survival, improvement in quality of life (asthenia, cognitive and psychiatric dysfunction, flushing, itching, diarrhoea and weight loss) and reduced risk of anaphylaxis.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The only approved drug for aggressive systemic mastocytosis is midostaurin. Other off label interventions include imatinib (for about 5% patients lacking the KIT D816V mutation) and other cytoreductive interventions administered by haematologists and oncologists. Symptom controlling medication with anti-mast cell mediator drugs may be optimised by allergists and dermatologists.
9a. Are any clinical guidelines used in the	Not aware of any but please consult haematology

treatment of the condition, and if so, which?	
9b. 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.)	Symptomatic control of anaphylaxis, skin, bowel, psychiatric, and osteopenia/porosis follow specialty-defined pathways by relevant clinicians and those with a special interest in mastocytosis
9c. What impact would the technology have on the current pathway of care?	Provide an approved alternative to midostaurin for patients with advanced multisystem mastocytosis. Comparative studies of efficacy and disease remission are not available but phase 3 studies indicate good tolerance and side effect profile for avapritinib
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	See 9c. It is expected that the need for symptomatic care will be reduced following a good response to avapritinib
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist services centred on haematology with multidisciplinary input, as now
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None additional

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes for patients with advanced systemic mastocytosis who are intolerant of midostaurin
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Advanced systemic mastocytosis is a rare condition that requires management in specialist centres

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Blood monitoring in secondary and primary care

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Evidence of organ dysfunction and treatment response
15. 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?	Improvement in appearance of skin lesions, and potential reduction in risk of anaphylaxis
16. 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
16a. Is the technology a 'step-change' in the management of the condition?	Yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Symptom burden, reduced quality of life and survival
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Possible need for treatment withdrawal

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in disease survival, reduction in disease progression and improved symptom control. Yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Tryptase level, reflects overall mast cell burden
18d. Are there any adverse effects that were	Not known

not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA728]?	No
21. How do data on real-world experience compare with the trial data?	Information not available to me since I do not lead on the management of patients with advanced systemic disease

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Novel treatment for a rare fatal illness with high disease burden - improved overall survival and reduced disease progression • Improved symptom control • Improved quality of life • Good safety profile • Well tolerated overall

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External Assessment Group Report
Avapritinib for treating advanced systemic mastocytosis [ID3770]

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Lucy Shepherd performed the critical review of the clinical effectiveness evidence and indirect treatment comparisons and drafted Sections 2 and 3 of the report.
Thai Han Phung performed the critical review of the economic analyses, validated the economic model, conducted the EAG additional analyses and contributed to drafting Sections 4 and 7 of the report.
Naomi Kate Gibbs performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.
Ros Wade performed the critical review of the clinical effectiveness evidence and drafted Sections 2 and 3 of the report.
Minyue Gao performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 6 of the report.
Helen Fulbright reviewed the company's search strategies and provided editorial support.
Claire Rothery performed the critical review of the economic analyses, conducted the EAG additional analyses, contributed to drafting Sections 4, 5, 6 and 7 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.
Sofia Dias provided advice, commented on drafts of the report and takes joint responsibility for the report as a whole.

Note on the text
All commercial-in-confidence (CIC) data have been [redacted].

Table of Contents

Table of Tables

Table of Figures

List of Abbreviations

1L	First line of therapy
2L+	Second or later line of therapy
AdvSM	Advanced systemic mastocytosis
AdvSM-SAF	Advanced systemic mastocytosis Symptom Assessment Form
AE	Adverse event
AESI	Adverse event of special interest
AHN	Associated haematological neoplasm
Allo-HSCT	Allogenic haematopoietic stem cell transplant
ASM	Aggressive systemic mastocytosis
BAT	Best available therapy
CHE	Centre for Health Economics
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRh	Complete response with partial recovery of peripheral blood counts
CS	Company submission
CSR	Clinical study report
CUP	Compassionate use program
DOR	Duration of response
DOT	Duration of treatment
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECS	External control study
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire
ESS	Effective sample size
FAS	Full-analysis set
HCHS	Hospital and community health services
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
ICC	International Consensus Classification
ICER	Incremental cost-effectiveness ratio
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue
KM	Kaplan-Meier
LOT	Line of therapy
MAIC	Matching-adjusted indirect comparison
MCL	Mast cell leukaemia
MHRA	Medicines and Healthcare products Regulatory Agency
mIWG-MRT-ECNM	Modified International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall response rate

OS	Overall survival
PAS	Patient Access Scheme
PartSA	Partitioned Survival Analysis
PD	Progressive disease
PEP	Primary efficacy population
PFS	Progression-free survival
PGIS	Patient Global Impression of Symptom Severity
PPRE	Pure Pathological Response-Evaluable
PR	Partial remission
PR	Partial response
PSSRU	Personal Social Service Research Unit
QALY	Quality-Adjusted Life Year
RAC-RE	Response Assessment Committee Response-Evaluable
RCT	Randomised controlled trial
RWE	Real world evidence
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with associated haematological neoplasm
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TOT	Time on treatment
TRAE	Treatment-related adverse event
TSS	Total symptom score
TTR	Time to response
UK	United Kingdom
WHO	World Health Organization

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Data presented in the company submission (CS) are primarily from the ongoing PATHFINDER study, using the September 2022 data cut-off. In response to the EAG's clarification questions, the company stated that an additional data cut-off was available (September 2023) and further details and updated analyses would be provided "at a later date". However, none of the key analyses were updated with the September 2023 data. In addition, a number of interpretation and reporting errors have been identified within the company submission. While many of these were corrected at the clarification stage, additional errors were identified within the CS and supporting documents at a later stage.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID3770	Summary of issue	Report sections
1	Lack of clarity of what constitutes "best available therapy" at second or subsequent lines	3.1.5, 3.6
2	Separation of the population by treatment line	4.2.3, 4.2.4
3	Limitations of the effectiveness evidence	3.6
4	Limitations of the indirect treatment comparisons	3.4, 3.6
5	Lack of consistency in the source of evidence used to inform the different survival parameters in the model	4.2.6.2
6	Immaturity of the overall survival data used in the extrapolations	4.2.6.2
7	Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS	4.2.6.2
8	Source of evidence used to inform time on treatment in the model	4.2.6.2
9	Uncertain duration of treatment benefit for avapritinib	4.2.6.2
10	Exclusion of subsequent therapy costs	4.2.6.2
11	Uncertainty in the progression-free and progressive disease health state utility values	4.2.8.2

There are two key differences between the EAG's preferred assumptions and the company's preferred assumptions:

(i) Time on treatment (TOT), i.e., the expected duration on treatment until discontinuation due to disease progression or intolerability, in the EAG's base case is based on data from PATHFINDER (safety population) for avapritinib, adjusted for inverse probability of treatment weighting (IPTW) with the historical external control study (ECS), while the ECS IPTW analysis is used for TOT for comparators; in the company's base case, TOT is sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the compassionate use program (CUP), while unweighted data from the ECS is used for the comparators.

(ii) The treatment-specific TOT curves provide a proxy for progression-free survival (PFS) for avapritinib and the comparators in the EAG's base case because PFS data is not available from the ECS and the PFS data from PATHFINDER (Response Assessment Committee Response-Evaluable, RAC-RE population) for avapritinib is unreliable; in the company's base case, the TOT curve is used as a proxy for the comparators only, while PFS data from the RAC-RE population (unweighted analysis) of PATHFINDER is used for avapritinib.

The EAG identified other key uncertainties, which the EAG is unable to resolve based on the data currently available. These are described further in the sections below.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who are alive (overall survival, OS) and progression-free (PF) over time, which is associated with improved health-related quality of life relative to the comparators.
- Allowing a proportion of the cohort in the avapritinib arm to discontinue treatment before disease progression, while for the comparator arm PFS is assumed to be the same as TOT, i.e., the model assumes that patients in the comparator arm discontinue treatment due to disease progression only, which means that no part of the cohort is 'off treatment' before progression. In the model, the utility values for PF are applied for the total cohort progression-free; therefore, avapritinib is modelled to receive QALY gains compared to the comparators for patients who interrupt treatment before progression.
- Applying a duration of treatment benefit of 5 years for avapritinib.

Overall, the technology is modelled to affect costs by:

- Increasing the TOT compared to the comparators, with associated drug acquisition and adverse event costs (noting that the largest component of cost difference between avapritinib and its comparators is drug acquisition costs).
- Increasing the proportion of the cohort PF, with associated resource use consumption, while decreasing the proportion of the cohort with progressive disease (PD) and need for palliative care at end of life.

The two critical parameters in the partitioned survival analysis impacting the cost-effectiveness of avapritinib relative to the comparators are: (i) time on treatment; and (ii) duration of avapritinib survival benefit. TOT determines the duration of therapy with associated drug acquisition costs, which represent the largest component of cost difference between avapritinib and its comparators; and TOT provides a proxy for PFS, which in turn drives the treatment costs and the duration of health-related quality of life benefits associated with PFS compared to PD. The duration of benefit affects the long-term survival gains (both OS and PFS) associated with avapritinib relative to the comparators.

The modelling assumptions that have the greatest effect on the ICER are:

- The OS extrapolation which affects the magnitude of the OS benefit for avapritinib relative to the comparators.
- The duration of treatment survival benefit for avapritinib of 5 years.
- The source of evidence used to inform TOT in the model, i.e., data from PATHFINDER (safety population), adjusted for IPTW with the historical ECS, for avapritinib and the ECS IPTW analysis for comparators versus UK CUP for avapritinib and unweighted ECS for comparators.
- Use of TOT curves as a proxy for PFS for both avapritinib and the comparators versus using the PFS curve for avapritinib and the TOT curve for the comparators. Note that this inconsistency means that a proportion of the avapritinib cohort can discontinue treatment before disease progression, while no part of the cohort for comparators can discontinue treatment before progression.
- Utility values for PF and PD health states.

1.3 The decision problem: summary of the EAG's key issues

Key issues related to the decision problem include the lack of comparative evidence on key outcomes, and a lack of clarity of what constitutes best practice at second or subsequent lines of therapy in the NHS.

Issue 1 Lack of clarity of what constitutes "best available therapy" at second or subsequent lines

Report section	**3.1.5, 3.6**
Description of issue and why the EAG has identified it as important	The main comparator for avapritinib is midostaurin as a first-line (1L) treatment option. Best available therapy (BAT) is the comparator at second or subsequent lines (2L+) of therapy. However, this comprises a range of off-label therapies including imatinib, interferon alpha and other off-label therapies not included in the NICE scope. It also includes midostaurin, which is typically given at first line.
What alternative approach has the EAG suggested?	That midostaurin be excluded from BAT.
What is the expected effect on the cost-effectiveness estimates?	OS is expected to be less for BAT with the exclusion of midostaurin; however, prior midostaurin use in approximately 80% of patients in the 2L+ population in PATHFINDER may have had an impact on survival outcomes for avapritinib in the 2L+ population, which has not been assessed by the company.
What additional evidence or analyses might help to resolve this key issue?	Clear evidence on what therapies are given in the NHS after midostaurin and the proportion of patients receiving midostaurin as second or subsequent line therapy. Analyses using comparator arm data of sufficient sample size including only patients receiving therapies that reflect NHS practice may help resolve this issue.

Issue 2 Separation of the population by treatment line

Report section	4.2.3 and 4.2.4
Description of issue and why the EAG has identified it as important	Limited justification for the separation of the population by treatment line, whereas the NICE recommendation for midostaurin is not restricted to the 1L population. The EAG considers that the separation of the population by treatment line has resulted in treatment comparisons that are determined by increasing the sample size due to the immaturity of the available survival data (e.g., including a larger cohort of 2L+ BAT) rather than reflecting the likely treatment pathway for AdvSM in the UK.
What alternative approach has the EAG suggested?	The EAG believes that there is merit in assessing the cost-effectiveness of avapritinib compared with midostaurin in the overall population, i.e., not separated by line of treatment. This would involve using data from the entire ECS for midostaurin, who had received ⩾1 line of systemic therapy (not necessarily as 1L) for AdvSM and data for avapritinib from PATHFINDER (and/or combined with EXPLORER 200 mg OD), with an adjustment made to balance for differences in treatment lines using the propensity weights; this also avoids discarding data by prior use of systemic therapies, which is necessary when splitting the data by treatment line.

What is the expected effect on the cost-effectiveness estimates?	Unknown as not assessed by the company.
What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see an analysis comparing avapritinib with midostaurin in the full population for all treatment lines, with an adjustment made to balance for differences in treatment lines using propensity weights in the IPTW; additional data from EXPLORER 200 mg OD (n=20) may support this analysis by increasing the available sample size for avapritinib, as used in the company's MAIC analysis.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The clinical effectiveness evidence is limited. There are no studies comparing avapritinib to the relevant comparators. Available evidence is from ongoing single arm studies for which evidence is still immature. Indirect comparisons also have important limitations.

Issue 3 Limitations of the effectiveness evidence

Report section	**3.6**
Description of issue and why the EAG has identified it as important	There are no comparative studies of avapritinib. The effectiveness evidence comes from two single arm studies, of which one is completed and one is still ongoing and results are immature. The main source of evidence is an uncontrolled study where 105 of 107 patients received 200 mg avapritinib, additional evidence is provided from another uncontrolled study in patients receiving a range of doses (data from the small number of patients [n = 20] receiving 200 mg of avapritinib are available). Data on overall survival is sparse since not many events had occurred at the data cut presented by the company. The lack of long-term data is a limitation. A more recent data cut is available but updated analyses were not provided to the EAG.
What alternative approach has the EAG suggested?	Analyses with the latest available data cut (2023) may help reduce some of the uncertainty due to immaturity.
What is the expected effect on the cost-effectiveness estimates?	Unknown. EAG scenarios show that the cost-effectiveness results are highly sensitive to the OS extrapolations used in the model. See issue 6 below.
What additional evidence or analyses might help to resolve this key issue?	The lack of a randomised comparative study is a limitation. Updated analyses with the latest data cut would help mitigate the uncertainty due to data maturity.

Issue 4 Limitations of the indirect treatment comparisons

Report section	**3.4, 3.6**
Description of issue and why the EAG has identified it as important	There are uncertainties in the indirect comparison owing to limited reporting and inappropriate adjustment for baseline characteristics. It is difficult to

	determine the reliability of the relative effectiveness estimates in the IPTW and MAIC as there is a lack of comparable analyses that could be used to compare two indirect treatment comparison (ITC) methods relevant for this appraisal (using a population of patients receiving 200 mg avapritinib only). The IPTW analyses performed to compare avapritinib to midostaurin or best available therapy could not provide estimates of progression-free survival (Section 4.2.4). The MAIC report provided an exploratory analysis on the relative efficacy of PFS comparing avapritinib and midostaurin which could have informed relative efficacy of avapritinib versus midostaurin at first-line, but this was not described in the CS nor incorporated into the economic model.
What alternative approach has the EAG suggested?	Appropriate justification of characteristics adjusted for in each analysis. Where possible, the consistent use of relevant prognostic characteristics adjusted for in the IPTW and MAIC, updated analyses using the latest data cut-offs, and analyses focusing solely on patients receiving 200 mg avapritinib.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Providing comparable analyses of populations who received 200 mg avapritinib in the MAIC and IPTW would improve certainty in the relative efficacy estimates of the ITCs. An exploration of potential alternative external control studies where some measure of progression is available using IPTW methods may be useful.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Lack of consistency in the source of evidence used to inform the different survival parameters in the model

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	There is a lack of consistency in the sources of data used to inform the different survival parameters in the model. The company uses the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW for the comparisons with the relevant comparators in the 1L and 2L+ populations, but uses the RAC-RE population unweighted analysis for PFS for avapritinib (due to the absence of PFS data collected in ECS and safety population). More importantly, however, the TOT curve for avapritinib, which determines the time until treatment discontinuation due to disease progression or other reasons, is not informed by PATHFINDER and is therefore not consistent with the PFS and OS outcomes used in the model. Furthermore, the approach used to determine the probability of moving to the progressive disease health state, via the PFS and OS curves,

	differs for avapritinib and the comparators, where the TOT curve is used as a proxy for PFS for the comparators but not for avapritinib. This mismatch of different sources of evidence to inform three inter-related parameters in the model (PFS, TOT and OS) is a major concern because it creates inconsistencies in the data used.
What alternative approach has the EAG suggested?	Consistent source of data used to inform the survival parameters in the model. The EAG considers that the PATHFINDER safety population for avapritinib, adjusted for IPTW for the comparisons from the ECS should be used, where possible, to ensure consistency with OS in the model.
What is the expected effect on the cost-effectiveness estimates?	TOT sourced from PATHFINDER IPTW analysis has a significant impact on the cost-effectiveness estimates because median TOT in PATHFINDER was longer than estimates from the UK CUP for avapritinib. The incremental costs increase significantly because patients remain on treatment for longer. See issue 8 below.
What additional evidence or analyses might help to resolve this key issue?	More mature OS, PFS and TOT data from the same population for use in the model.

Issue 6 Immaturity of the OS data used in the extrapolations

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The OS data used in the company's base case analysis from PATHFINDER at the September 2022 data cut-off is immature, with median OS not reached in either population. The immature OS data is extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which lead to very different long-term survival outcomes. The EAG is particularly concerned about the accuracy of the substantial OS benefit for avapritinib compared to midostaurin in the 1L population, which only falls at 5 years because of the finite duration of treatment benefit assumption. The EAG notes that there is an interplay between the survival outcomes in the model and the duration of treatment benefit assumed for avapritinib.
What alternative approach has the EAG suggested?	The EAG emphasises the need to have more mature OS data to inform the model fitting and extrapolations over time because without this data, the reliance on immature survival outcomes may result in highly inaccurate estimates of survival benefit for avapritinib compared to the comparators in both populations.

What is the expected effect on the cost-effectiveness estimates?	The extent to which the different parametric extrapolations have an impact on the cost-effectiveness results is contained by the inclusion of a finite duration of treatment benefit of 5 years for avapritinib. EAG Scenarios 7-10 demonstrate the interplay between the duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered; the results show that [redacted] for the comparison of avapritinib with 1L midostaurin are highly sensitive to these assumptions[redacted]. Scenarios 7a and 7b show that the cost-effectiveness results are highly sensitive to the joint parametric survival extrapolations used for OS and TOT in the comparison of avapritinib with 2L+ cladribine and, to a lesser extent, in the comparison with 2L+ BAT.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the updated data cut-off from PATHFINDER (September 2023) may help reduce uncertainty in OS estimates and may relieve some of the EAG's concerns in relation to the maturity of the data.

Issue 7 Limited availability of PFS data and use of TOT as a proxy for PFS

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	PFS was not available from the ECS to enable an IPTW comparison with PATHFINDER. Therefore, the company uses the comparator's TOT curve as a proxy for the comparator's PFS curve, but not for avapritinib. As a consequence, patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression, whereas avapritinib is modelled to receive QALY gains for patients who interrupt treatment before progression, with no treatment costs after discontinuation. This inconsistency in the approach used for avapritinib and the comparators is a key driver of the cost-effectiveness results, particularly for the comparison of avapritinib with 1L midostaurin because the area between the PFS and TOT curves for avapritinib in this comparison is substantial. Furthermore, the PFS data from the RAC-RE population (unweighted analysis) of PATHFINDER is inconsistent with the OS data from the safety population (IPTW sample) of PATHFINDER used in the company's base case analysis. As a result, for the comparison of avapritinib with 1L midostaurin, no proportion of the cohort in the avapritinib arm enters the progressive disease health state in the first 5 years of the model, i.e., the treatment benefit from initiating

	treatment with avapritinib is maintained for a full 5 years without any disease progression.
What alternative approach has the EAG suggested?	The EAG considers that the only reasonable approximation for PFS in the absence of alternative reliable estimates is to use the TOT curve as a proxy for PFS in both the avapritinib and comparator arms in the model, which ensures consistency across the intervention and comparators and ensures consistency with OS in the model when TOT is sourced from PATHFINDER (avapritinib).
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 2 shows an [redacted] and a reduction in the incremental QALYs because no proportion of the avapritinib cohort discontinues treatment before disease progression, as permitted in the company's base case.
What additional evidence or analyses might help to resolve this key issue?	More mature PFS and TOT data from the same population for use in the model. The EAG considers that the updated data cut-off from PATHFINDER (September 2023) may help reduce uncertainty in PFS and TOT estimates and may relieve some of the EAG's concerns in relation to the maturity of the data.

Issue 8 Source of evidence used to inform time on treatment in the model

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	TOT for avapritinib is sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the CUP. The EAG considers the choice of TOT curve for avapritinib as a major limitation of the company's base case analysis because: (i) it is not consistent with the OS outcomes used in the model; (ii) it is based on a very small cohort of 13 patients and only 9 of these patients received the starting dose of avapritinib 200 mg OD; (iii) the data is not separated by treatment line as required by the model because 10 out of the 13 patients received avapritinib as a first line regime; (iv) KM data for duration of therapy in CUP is not available and therefore the company applied a simple exponential distribution to the median duration of treatment to derive a parametric curve over time; and, importantly, (v) an IPTW ITC of avapritinib and the comparators is not used for the TOT curves in the model.
What alternative approach has the EAG suggested?	TOT curve for avapritinib based on extrapolating the Kaplan-Meier data for duration of treatment from PATHFINDER safety population (to match the population used for OS) adjusted for IPTW with the ECS, and the IPTW sample from the ECS for TOT for the comparators rather than the unweighted median duration of therapy (with simple exponential distribution applied to the median duration) as used in the company's base case.
What is the expected effect on the cost-	The resulting impact on the cost-effectiveness estimates is significant because median TOT in PATHFINDER was longer than estimates from the UK CUP for avapritinib. EAG Scenario 1 demonstrates that the incremental costs increase significantly because patients remain on treatment for

effectiveness estimates?	longer [redacted].
What additional evidence or analyses might help to resolve this key issue?	Mature data on duration of therapy.

Issue 9 Uncertain duration of treatment benefit for avapritinib

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The duration of treatment benefit for avapritinib is uncertain. This is assumed to be 5 years in the model based on the rate of duration of response in PATHFINDER of 70.5% (95% CI, 43.5 – 97.4%) at 42 months in the RAC-RE population for all AdvSM patients. The EAG considers the assumption of a 5-year treatment benefit for avapritinib to be reasonable in the 1L population but acknowledges that this could potentially be pessimistic when using the TOT curves from the parameterised IPTW outcomes from PATHFINDER and the ECS for avapritinib, where approximately [redacted] of patients remain on treatment at 5 years. However, the EAG notes that there is an interplay between the survival parameters in the model of OS and PFS (informed by TOT) and the duration of treatment benefit assumed for avapritinib. Therefore, it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes assumed in the model; for example, if the extrapolation of OS based on immature data is highly optimistic, then an appropriate cap on the duration of treatment benefit is required.
What alternative approach has the EAG suggested?	Consideration of a longer duration of treatment for avapritinib in the 1L population, assuming that the response to treatment is maintained for longer and patients remain on treatment for longer as a consequence.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenarios 4-6 show that when the duration of treatment effect is longer of 7.5 years, 10 years and lifetime, respectively, avapritinib appears more cost-effective than 1L midostaurin (holding the survival outcomes the same as the base case). However, EAG Scenarios 7-10 demonstrate the interplay between the duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered; the results show that [redacted] are highly sensitive to these assumptions.

What additional evidence or analyses might help to resolve this key issue?	Long-term data on the duration of avapritinib benefits is required.

Issue 10 Exclusion of subsequent therapy costs

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment is not considered in the company's base case analysis in the 1L or 2L+ populations. The EAG is concerned that there may be potential confounding of subsequent treatment effects on survival outcomes reported in PATHFINDER for avapritinib, but that the costs (and utility values) associated with the use of subsequent therapies are excluded from the model. This is expected to only represent a concern for the proportion of the cohort who received allo-HSCT because other treatments options used post-progression would be expected to be the same for avapritinib and its comparators, and the cap of 5 years on the duration of treatment benefit for avapritinib means that there is no long-term differential in post-progression survival between avapritinib and the comparators in the model.
What alternative approach has the EAG suggested?	Consideration of post-progression survival outcomes and costs of subsequent treatment use.
What is the expected effect on the cost-effectiveness estimates?	Unknown, but if use of subsequent therapies (particularly, allo-HSCT) have an impact on survival outcomes included in the model, the corresponding costs have been excluded from the company's base case analysis. Inclusion of the costs of allo-HSCT would reduce the cost-effectiveness of avapritinib relative to its comparators.
What additional evidence or analyses might help to resolve this key issue?	Information on treatments used post-avapritinib discontinuation from PATHFINDER and numbers of patients eligible to receive allo-HSCT. Additional evidence on post-progression survival outcomes.

Issue 11 Uncertainty in the PF and PD health state utility values

Report section	4.2.8.2
Description of issue and why the EAG has identified it as important	The utility values for the PF and PD health states are uncertain. The utility data is based on the PATHFINDER September 2022 data cut-off (i.e., not the latest September 2023 data cut-off) where there are a limited number of observations at each time point used to inform the mapped utility value associated with PF in

	the 1L and 2L+ populations, with missing data from the EORTC QLQ-C30 domains excluded from the analysis and no consideration given to data imputation methods. The EAG has a number of concerns about the PD/PF utility ratio used in the company's analysis to derive a utility value for PD, including (i) generalisability of the utility values for patients with AML to those with AdvSM; (ii) large variability in the PD/PF utility ratios across the four included studies, ranging from 0.41 to 0.99; (iii) the mean age in all four studies is much lower than the modelled population; and (iv) it is uncertain whether the estimated PD/PF utility ratio is equally applicable to the 1L and 2L+ populations as assumed in the company's base case analysis.
What alternative approach has the EAG suggested?	The EAG explores the impact of varying the PF utility value on the cost-effectiveness results, which also changes the PD utility value because the PD/PF utility ratio (also uncertain) is applied to the PF utility value.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 11 shows that the total QALYs are highly sensitive to the utility values used in the model, where a relatively small change in the PF utility value of [redacted] (corresponding to a change of [redacted] in the PD utility value) for the 1L comparison, results in a significant reduction in incremental total QALYs for avapritinib compared with midostaurin. Similarly, a relatively small change in the PF utility value of [redacted] (corresponding to a change of [redacted] in the PD utility value) for the 2L+ population, results in a significant reduction in incremental total QALYs for avapritinib compared with 2L+ cladribine and 2L+ BAT, with corresponding ICER increase of [redacted] and [redacted], respectively, compared to the EAG's preferred base case.
What additional evidence or analyses might help to resolve this key issue?	Health-related quality of life data for patients in a pre- and post-progression health state. Data from EXPLORER could potentially augment the existing sample size by an additional 16 patients with EORTC QLQ-30 Global Health Score, which would supplement the small cohorts of 29 patients for the 1L population and 46 patients for the 2L+ population from PATHFINDER.

1.6 Other key issues: summary of the EAG's view

No other key issues identified.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the EAG's preferred assumptions and resulting ICER for the comparison of avapritinib with midostaurin in a population who have not received prior systemic therapies (1L population). Table 3 summarises the EAG's preferred ICER for the comparison of avapritinib with cladribine in a population who have received prior systemic therapies (2L+ population), while Table 4 presents the results for the comparison of avapritinib with best available therapy (BAT) in the 2L+ population, where BAT is a mixture of therapies (including midostaurin and cladribine) and represents a proxy for 2L+ cladribine.

Table 2 EAG's preferred base case for the comparison of avapritinib with 1L midostaurin

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case (following response to EAG points for clarification)	[redacted]	2.27	[redacted]
EAG's preferred base case (TOT as proxy for PFS for avapritinib and comparators and TOT based on IPTW analysis from PATHFINDER and ECS)	[redacted]	1.98	[redacted]

Table 3 EAG's preferred base case for the comparison of avapritinib with 2L+ cladribine

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case (following response to EAG points for clarification)	[redacted]	1.09	[redacted]
EAG's preferred base case (TOT as proxy for PFS for avapritinib and comparators and TOT based on IPTW analysis from PATHFINDER and ECS)	[redacted]	1.01	[redacted]

Table 4 EAG's preferred base case for the comparison of avapritinib with 2L+ BAT

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case (following response to EAG points for clarification)	[redacted]	1.33	[redacted]
EAG's preferred base case (TOT as proxy for PFS for avapritinib and comparators and TOT based on IPTW analysis from PATHFINDER and ECS)	[redacted]	1.21	[redacted]

Modelling errors identified and corrected by the EAG are described in Section 5. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.1.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission to NICE on the clinical and cost-effectiveness of avapritinib (Ayvakyt®) for treating advanced systemic mastocytosis (AdvSM).

Avapritinib is a type 1 tyrosine kinase inhibitor (TKI) that inhibits *KIT* D816V-mediated mast cell activation and proliferation. Avapritinib received European Medicines Agency (EMA) marketing authorisation in March 2022 as a monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), after at least one systemic therapy. Avapritinib does not currently have a marketing authorisation in the United Kingdom (UK) for treating AdvSM. Treatment with avapritinib is not recommended in AdvSM patients with a platelet count < 50 x 10^9/L.

2.2 Background

2.2.1 Disease background

Advanced systemic mastocytosis is a rare haematological neoplasm characterised by the uncontrolled accumulation of mast cells which results in damage to organs across the body. AdvSM represents the more aggressive and life-threatening forms of systemic mastocytosis (SM) and accounts for ~10% of patients with SM.[1, 2] There are three types of AdvSM that can occur: ASM, SM-AHN and MCL.

Blueprint Medicines commissioned a report of hospital episode statistics (HES) data to provide details of the epidemiology of AdvSM in England.[3] The incidence of AdvSM in 2022 was [redacted] per 1 million people, equating to [redacted] new cases of AdvSM in England every year. In this cohort, the majority of patients were diagnosed with ASM ([redacted]), [redacted] were diagnosed with SM-AHN and [redacted] were diagnosed with MCL.

Mutations to the *KIT* gene are linked to the aetiology of AdvSM, especially the *KIT* D816V mutation (which is found in 90-95% of cases[4]). The mutation to the *KIT* gene leads to constitutive activation of the *KIT* receptor, triggering signalling pathways leading to cell proliferation and accumulation of mast cells in organs and tissues.[5] The increased mast cell burden in organs and tissues results in a range of clinical manifestations, including gastrointestinal, musculoskeletal, cardiac, cutaneous and respiratory symptoms, and neurocognitive issues. AdvSM is associated with poor survival outcomes; median overall survival (OS) is 5.7 years (95% confidence interval [CI]: 0.6, 4.5) for ASM, 2.9 years (95% CI: 2.5, 3.3) for SM-AHN and 1.9 years (95% CI: 0, 5.2) for MCL.[2] It is worth noting that these

survival data are from a study of patients diagnosed with mastocytosis between 1978 and 2017, therefore outcomes are likely to be improved with the introduction of newer therapies since these results were published.

2.2.2 Clinical pathway of care

2.2.2.1 Diagnosis

Diagnosis of AdvSM is complex, and relies on an initial diagnosis of SM, which is based on World Health Organization (WHO) criteria[6] and the International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias.[7] Diagnostic criteria for SM are described in Table 4 of the CS. Following this, additional diagnostic criteria are used for the three subtypes of AdvSM[8] (summarised in Figure 4 of the CS).

- **ASM:** identification of one or more C-findings (which indicate organ damage from the infiltration of mast cells)
- **SM-AHN:** a diagnosis of SM alongside a diagnosis of associated haematological neoplasm (AHN) (based on WHO criteria). Patients with SM-AHN may also present C-findings.
- **MCL:** presents with increased levels of mast cell infiltration into the bone marrow (proportion of mast cells in bone marrow aspirate is ≥20%. Patients with MCL may also present C-findings.

2.2.2.2 Treatment guidelines

There are no current treatment guidelines for AdvSM in the UK. Clinical experts to the company have provided their opinions on the current treatment pathway for AdvSM in the UK (Figure 5 of the CS). To summarise, following confirmation of diagnosis, patients requiring disease-modifying therapy receive midostaurin as a first-line treatment option. For patients with SM-AHN, if the AHN requires more immediate treatment, that would be treated with chemotherapy such as azacitidine, prior to receiving midostaurin. Off-label therapies may be considered for use in patients with AdvSM, including cladribine, imatinib and pegylated interferon/interferon alpha. Cladribine is a chemotherapeutic agent and is given as a short-course of treatment (for a set number of cycles) as a second-line therapy, or may be considered for patients with high-bulk disease or who are ineligible for midostaurin. Imatinib may be used for patients who do not have the *KIT* D816V mutation as a third-line therapy. Interferon alpha can be used for AdvSM patients, but its use is minimal (6% in a real world study of centres across Europe[9]). Pegylated interferon may be used for AdvSM patients with bone disease, or in progressive disease after all other therapies have been tried, again its use is minimal (4% across Europe[9]).

Midostaurin is the only treatment that has been appraised by NICE for AdvSM and was recommended for use in the NHS in August 2021 for adult patients with ASM, SM-AHN or MCL (technical appraisal (TA) 728).[10] The appraisal was based on two trials of midostaurin – A2213 and D2201 (described in Section 3.3.2), which were compared to two non-randomised studies – a German registry (Reiter et al., 2017)[11], and a compassionate use programme and registry study (CEREMAST)[12, 13]. The committee considered that the two midostaurin trials were generalisable to the NHS and were relevant for decision making, and that the study by Reiter et al. (2017) was the most relevant comparator.[10] The key issues regarding this appraisal surrounded the uncertainty of efficacy data in the indirect treatment comparison owing to differences in the populations and difficulties with adjustment, utility estimates that didn't fully capture benefits from midostaurin, and uncertainty with the duration of treatment benefit.[10]

Allogenic haematopoietic stem cell transplant (allo-HSCT) can be a curative therapy for patients with AdvSM. However, stringent eligibility criteria mean that a very limited number of patients receive allo-HSCT. Clinical advice to the EAG suggested that allo-HSCT would only be offered to younger patients with good organ function who were in remission (or had at least a partial response) following previous therapy, and therefore is only an option for around 5% of patients.[14]

Blueprint medicines propose that avapritinib should be primarily used as a first-line treatment option for patients with AdvSM requiring disease-modifying therapy. Clinicians' advice to the company considered that avapritinib would be used in preference to midostaurin, unless contraindicated and would therefore mainly displace midostaurin at first line. The EAG's clinical advisors confirmed that the clinical pathway of care presented in the CS is generally reflective of current NHS practice and the proposed positioning of avapritinib appears appropriate.

2.3 Critique of company's definition of decision problem

A summary and critique of the company's definition of the decision problem is presented in Table 5.

Table 5 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with advanced systemic mastocytosis	Adults with advanced systemic mastocytosis	Not applicable	The population described in the CS is in line with the NICE scope. The characteristics of patients in the PATHFINDER and EXPLORER studies are similar to the NHS advanced systemic mastocytosis population (see Section 3.2).
Intervention	Avapritinib	Avapritinib	Not applicable	The intervention described in the CS is in line with the NICE scope.
Comparator(s)	• Midostaurin • Cladribine • Imatinib • Interferon alpha	• Midostaurin • Cladribine	The main comparator for avapritinib is midostaurin. Midostaurin is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), and is recommended by NICE in this indication. ASM, SM-AHN and MCL are collectively known as advanced systemic mastocytosis (AdvSM). No other treatments have regulatory approval in the UK or are recommended by NICE for the treatment for AdvSM. Midostaurin is therefore the current standard of care and constitutes established clinical practice for patients with AdvSM in England. Off-label cladribine is no longer commonly used to treat patients with AdvSM in the UK but may be used in patients who require rapid debulking or in patients who have to discontinue midostaurin due to tolerability issues. Data comparing avapritinib treatment with cladribine as second- or further-line (2L+) treatments have been included in this submission. Imatinib is not considered a relevant comparator for avapritinib in this submission. It is not routinely commissioned in the NHS in England for AdvSM and is used as an off-label therapy in a very small number of patients (2-3%) that do not have an activating *KIT* mutation (specifically the *KIT* D816V mutation which is	The EAG agrees that the main comparator for avapritinib is midostaurin as a first-line treatment option. Best available therapy (BAT) includes a range of off-label therapies that may be used as a second or later line of therapy, and is an appropriate comparator at 2nd line or later. The company's justification for excluding imatinib and interferon alpha appears appropriate, as they are used in only a small proportion of patients. However, these comparators (as well as other off-label therapies not included in the NICE scope) are represented in a comparison of outcomes in patients treated with BAT.

			responsible for approximately 95% of AdvSM cases). In analysis of Hospital Episode Statistics (HES) data (1 April 2018 to 31 March 2023), other than midostaurin, [redacted] of tyrosine kinase inhibitors (TKIs) for the treatment of AdvSM, including imatinib, was identified. It is noted that treatment for AdvSM may also include off-label use of pegylated interferon alpha, however, this treatment does not target the underlying cause of the disease has limited efficacy. Use of pegylated interferon alpha in the UK is extremely limited (4% of known lines of therapy in the real-world study were with pegylated interferon alpha). Whilst this submission does not include comparisons with imatinib and interferon alpha individually, they are represented in a comparison of outcomes in patients treated with best available therapy (BAT), which includes midostaurin and cladribine, as well as other off-label therapies not included in the scope of this submission.	
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • symptom severity adverse effects of treatment • health-related quality of life.	The following outcomes are presented: • overall survival • progression-free survival • response rate symptom severity • adverse effects of treatment • health-related quality of life • measures of mast cell burden	The outcome measures to be included in the company submission are in line with the final scope. In addition to the outcomes in the scope, measures of mast cell burden have been included to provide important additional evidence on the efficacy of avapritinib.	The outcomes presented in the CS are in line with the NICE scope. The primary endpoint of the PATHFINDER study was overall response rate (ORR), using the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis (mIWG-MRT-ECNM) measure of response. This is an appropriate measure of response and reflects the criteria used in clinical practice. However, important outcomes, such as progression-free survival, are not available for analyses based on the external control study (ECS), therefore, a proxy 'duration of treatment' has been used.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed	In line with NICE scope. A patient access scheme has been	Not applicable.	In line with NICE scope.

	in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	approved and is included within this submission.		
Subgroups	If evidence allows subgroup analysis by disease type to include: • aggressive systemic mastocytosis • systemic mastocytosis with associated haematological neoplasm • mast cell leukaemia	Although not a prespecified subgroup analysis, results by disease subtype are presented for the avapritinib studies.	To inform the economic analysis a comparative analysis by disease subtype would be required in treatment-naïve patients (first line of therapy [1L]) and separately in patients who previously received a systemic therapy (2L+). In the key trial underpinning the clinical efficacy of avapritinib (PATHFINDER), patient numbers in the ASM and MCL subtypes treated with avapritinib as a 1L or 2L+ therapy do not reach the minimal requirement to perform any statistical meaningful analysis. Therefore, comparative analyses were not carried out for the disease subtypes by line of therapy. The feasibility of comparing the three AdvSM subtypes in a matching-adjusted indirect comparison (MAIC) was investigated. In addition to the limitations regarding the number of patients available for this analysis, an adjusted comparison was not possible because the baseline	Subgroup analyses by disease subtype are presented for a number of clinical effectiveness outcomes: response to therapy, progression-free survival, overall survival and mast cell burden for the PATHFINDER Response Assessment Committee Response-Evaluable (RAC-RE) and EXPLORER populations. As the cost-effectiveness analyses are split by line of therapy, cost-effectiveness results of avapritinib by AdvSM disease types are not presented owing to limited sample sizes. Therefore, cost-effectiveness of avapritinib in each disease subtype is unclear.

			characteristics for each subtype were not reported in the comparator evidence.	
Special considerations including issues related to equity or equality	No issues relating to equity or equality raised in the scope.	Blueprint Medicines does not believe that the draft remit or scope will exclude people protected by equality legislation. However, it should be noted that, unlike midostaurin, avapritinib does not contain gelatine as an excipient.	Inclusion of gelatine can be problematic for people with certain religious or cultural beliefs, particularly those of the Islamic faith for whom this product may not be considered to be halal. Provision of a gelatine-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.	Clinical advisors to the EAG, who work at a centre with a multicultural patient population, had not experienced any patient not wishing to accept midostaurin treatment because it contains gelatine. Therefore, this issue is unlikely to impact a large proportion of advanced systemic mastocytosis patients in NHS practice.

Abbreviations: 1L, first line of therapy; 2L+, second- or further-line; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BAT, best available therapy; CS, company submission; EAG, External Assessment Group; ECS, external control study; HES, Hospital Episode Statistics; MAIC, matching-adjusted indirect comparison; MCL, mast cell leukaemia; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; RAC-RE, Response Assessment Committee Response-Evaluable; SM-AHN, systemic mastocytosis with associated haematological neoplasm; TKIs, tyrosine kinase inhibitors.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant clinical evidence relating to the efficacy and safety of treatments for adults with AdvSM. Details of the SLR are reported in Appendix D of the CS.

3.1.1 Searches

The SLR included searches to identify clinical evidence on avapritinib and relevant comparators in the treatment of adults with AdvSM. A description of the searches and all the search strategies are presented in Section D1.1.1, Appendix D of the CS. The EAG appraisal of the literature searching is presented in Appendix 1. In response to the EAG's clarification questions, the company provided additional information and corrections to errors identified by the EAG.

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the SLR of clinical effectiveness evidence are presented in Table 2 in Appendix D of the CS. Eligibility criteria relating to interventions of interest were broader than the decision problem addressed in the CS and included all approved or investigational pharmacological interventions used for the treatment of AdvSM; a total of 19 pharmacological treatments were listed.

Study selection was undertaken independently by two reviewers, with uncertainties checked by a third reviewer, minimising the possibility of errors or bias affecting the study selection process.

There were no randomised controlled trials (RCTs), all studies were prospective single arm studies or retrospective observational studies. There were four studies of avapritinib; PATHFINDER,[15] EXPLORER,[16] external control study[9] (ECS) and a report of a compassionate use program (CUP).[17] Only four prospective single arm studies (rather than retrospective observational studies) of comparator treatments were identified; two studies of midostaurin which were included in the matching-adjusted indirect comparison (MAIC) (D2201 and A2213[18, 19]), one study of cladribine,[20] and one study of interferon alpha.[21] The studies of cladribine and interferon alpha were not described further in the CS. In response to clarification question A7, the company stated that the study of cladribine was not described further because it did not report any relevant efficacy endpoints, therefore it could not be included in the MAIC.

3.1.3 Data extraction

Data extraction was undertaken by one reviewer using a standardised data extraction "shell" which was checked for accuracy by a second reviewer, reducing the potential for errors and bias. However, there were some errors in data extraction, which were corrected at the clarification stage. The proportion of patients in PATHFINDER with the *KIT* D816V mutation was incorrect in the table of baseline characteristics (Table 8 of the CS) and there were errors in the patient disposition table for PATHFINDER (Table 10 of the CS), these were corrected in response to clarification questions A14 and A15.

3.1.4 Quality assessment

Quality assessment was undertaken using an adapted version of the Downs and Black checklist,[22] which was appropriate, in view of the study designs. Quality assessment was undertaken as part of the data extraction process, using the same approach, reducing the potential for errors and bias. Quality assessment results for PATHFINDER, EXPLORER and the ECS are presented in Table 15 in Appendix D of the CS. The EAG requested clarification on some of the quality assessment judgements made by the company in relation to recruitment of patients in the ECS and losses to follow-up in all three studies (clarification question A8); the company reviewed their judgements and made corrections in their response to clarification questions. As acknowledged by the company, both PATHFINDER and EXPLORER are uncontrolled, single-arm studies with associated limitations.

3.1.5 Evidence synthesis

In the absence of within-study comparative evidence of avapritinib in the PATHFINDER and EXPLORER studies, pairwise meta-analyses were not possible. Therefore, indirect treatment comparisons (ITC) were conducted including an inverse probability of treatment weighting (IPTW) with a retrospective cohort – which compared avapritinib against midostaurin, cladribine and a basket of available therapies (the ECS) and a MAIC which compared the avapritinib studies against two midostaurin studies (A2213 and D2201). In the indirect treatment comparison analyses, results from the PATHFINDER and EXPLORER studies were pooled together. For the MAIC as reported in Pilkington et al. (2022), and initially provided in the company submission, the May/June 2020 data cut-offs were pooled, while in the most recent MAIC ITC report, provided at the clarification stage, the April 2021 data cut-offs were pooled. The company pool these studies to provide longer-term data on avapritinib in this population. The analyses used in the ITCs are described in detail in Section 3.4.

With the exception of midostaurin, which is predominantly used as a first-line therapy, there are no other treatments indicated for AdvSM. Therefore, a range of off-label therapies are often used at a second line or later, including cladribine, imatinib and interferon alpha (which were considered as relevant comparators in the NICE scope). Given the number of different therapies available, the

company group the off-label therapies together to create a BAT cohort. This approach is similar to that used in the midostaurin technology appraisal (TA728), where a pooled BAT comparator was considered appropriate by the committee.[11, 23] The BAT cohort in this appraisal was from the ECS and included patients who had received tyrosine kinase inhibitors (TKIs – 54% of 222 individual lines of therapy [LOT]) such as midostaurin and imatinib; cytotoxic therapies (41% of 222 individual LOT) such as cladribine and biologic therapies (11% of 222 individual LOT) including interferon-alpha and pegylated interferon. As midostaurin is most typically used in a first-line setting, the BAT was considered in comparisons at a second line or later. However, the BAT cohort also includes patients who received midostaurin as a second-line or later line of therapy ([redacted]), which is deemed by the EAG to not be representative of NHS practice (detailed further in Section 4.2.4.2).

3.1.6 EAG comments

The SLR appears to have been reasonably well conducted, although there were a number of minor errors, e.g., in reporting searches, tables of patients' baseline characteristics and patient disposition, and in quality assessment judgements, which were corrected by the company at the clarification stage. The main limitation of the SLR is the lack of high-quality comparative studies of avapritinib.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The company's efficacy and safety data were primarily based on the results of the ongoing Phase 2 single-arm PATHFINDER study.[15] Data were also presented from the Phase 1 dose-finding EXPLORER study.[16] An external control study[9] was undertaken to compare patients from the PATHFINDER and EXPLORER studies receiving avapritinib against a retrospective cohort of patients receiving AdvSM treatments used in clinical practice. Finally, brief results were presented from a report of 13 patients who received avapritinib in the UK via a compassionate use program.[17]

3.2.1 PATHFINDER

3.2.1.1 Design

PATHFINDER is an ongoing, phase 2, open label, single-arm study that informs the majority of the clinical effectiveness evidence of avapritinib in the CS. Patients with AdvSM were enrolled from the USA, Canada, and Europe (including the UK), to receive a starting dose of 200 mg of avapritinib, administered orally once daily. Patients with a confirmed diagnosis were enrolled into one of two cohorts:

- Cohort 1: AdvSM patients with ≥ 1 mIWG-MRT-ECNM criteria for evaluable disease, or have MCL

- Cohort 2: AdvSM patients who were not considered eligible for an adjudicated response and were confirmed to have ASM or SM-AHN, but were lacking evaluable C-findings

Following an eight-week screening period to assess eligibility, participants would enter a treatment period of at least 1 cycle (28 days). Following the last dose of avapritinib, participants would receive an end of treatment visit after 7-21 days. A safety follow-up consultation over the telephone was also given to check for resolution of any adverse events (AEs) 30 days after the last dose of avapritinib.

The primary efficacy endpoint of the study was overall response rate (ORR) based on the mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response. This primary outcome only applies to those in Cohort 1. ORR in AdvSM is defined as complete response (CR); complete response with partial recovery of peripheral blood counts (CRh); partial response (PR); or clinical improvement. Secondary endpoints include OS, PFS, symptom assessment (AdvSM-Symptom Assessment Form [SAF] total symptom score (TSS)) and other health-related quality of life (HRQoL) assessments.

In the CS, Blueprint Medicines provided the September 2022 PATHFINDER data cut-off. In response to the EAG's clarification questions, the company stated that an additional data cut-off was available (September 2023), but no updated analyses have been provided by the company.

3.2.1.2 Patients

The population eligible for avapritinib included adult patients diagnosed with either ASM, SM-AHN or MCL. For Cohort 1, patients must have had at least one of the specified C-findings measured by the mIWG-MRT-ECNM criteria. For all cohorts, patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status between 0 to 3. Important exclusion criteria for all cohorts included those with a history of a cerebrovascular accident or transient ischaemic attack within one year before the first dose of the study drug, known risk or recent history of intracranial bleeding or a platelet count <50,000μL. The EAG's clinical advisors considered that the study eligibility criteria were appropriate.

Baseline characteristics for PATHFINDER are presented for the September 2022 data cut-off in Table 8 of the CS, but are also summarised for the April 2021 data cut-off in Table 10 (in relation to the MAIC, which used the April 2021 data-cut offs; data provided in response to EAG clarification questions). Whilst only 9 patients were recruited from the UK, the EAG's clinical advisors considered that the characteristics of patients in PATHFINDER are similar to those seen in NHS practice.

Patient flow and discontinuations

Overall, 107 patients were enrolled onto PATHFINDER; of which 105 patients started avapritinib at a dose of 200 mg daily (the recommended starting dose) and two patients started avapritinib at a dose of

100 mg daily. Thirty-eight patients received avapritinib as a first-line therapy, and 69 received avapritinib as a second or later line of therapy (67 of which received a dose of 200 mg avapritinib).

In the CS, efficacy results are presented for two populations. The "safety population" included the 105 patients who received a starting dose of 200 mg avapritinib, of which 81 were response evaluable using mIWG-MRT-ECNM criteria, the "Response Assessment Committee Response-Evaluable (RAC-RE) population". Patient enrolment and disposition is summarised in the CS, Figure 9. Additional data were provided for the Pure Pathological Response Evaluable (PPRE) population following a clarification request by the EAG ([redacted]).[24] This population is similar to the RAC-RE population, except that they were not deemed evaluable per mIWG-MRT-ECNM criteria. Pure pathological response criteria are based on changes in bone marrow mast cells, serum tryptase levels and complete blood counts.[25] Baseline characteristics in the PPRE population (all treatment lines) are broadly similar to those in the RAC-RE and safety populations.

As of the September 2022 data cut-off, from the 105 patients treated with 200 mg avapritinib, 47 have discontinued treatment, and 34 have discontinued from the study. Therefore, 58 were still on avapritinib treatment at the data cut-off. Reasons for discontinuation were provided in Table 10 of the CS (corrected version provided in Table 5 of the clarification response document). At the clarification stage, the EAG requested clarification for some of the reasons for discontinuation from avapritinib and the study (Question A14). These are summarised for the safety population who received avapritinib at 200 mg in Table 6. Most common reasons for discontinuation from the treatment were [redacted], and the most common reasons for discontinuation from the study was [redacted].

After seeking further clarification from the company, the EAG considers that some of the reasons for discontinuation based on 'administrative/other' appear to be incorrectly categorised – for example including [redacted] in 'administrative/other' in the reasons for discontinuation of treatment, rather than [redacted]; or [redacted] being included in 'administrative/other' in the reasons for discontinuation of study, rather than [redacted].

Table 6. Reasons for discontinuation of treatment and study. Source: Clarification response Tables 4 and 5

	Safety Population (n = 105) n (%)
Discontinued from treatment	47 (44.8)
Continuing on treatment	58 (55.2)
Discontinued from study	34 (32.4)
Reasons for discontinuation of treatment	
Disease progression	[redacted]
AML	[redacted]
AE(s)	[redacted]

Related	[redacted]
Death	[redacted]
Lost to follow-up	[redacted]
Protocol deviation	[redacted]
Withdrew consent	[redacted]
Pregnancy	[redacted]
Investigator's decision	[redacted]
Administrative/other	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Sponsor Decision	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Reasons for discontinuation of study	
Disease progression	[redacted]
AE(s)	[redacted]
Death	[redacted]
Lost to follow-up	[redacted]
Protocol deviation	[redacted]
Withdrew consent	[redacted]
Pregnancy	[redacted]
Investigator's decision	[redacted]
Administrative/other	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Initiation of another antineoplastic therapy	[redacted]
Sponsor decision	[redacted]

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia.

3.2.1.3 Effectiveness

Efficacy data for PATHFINDER, from the September 2022 data cut-off, in patients who received a starting dose of 200 mg avapritinib (n = 105) are reported in Section B.2.6 of the CS. Data from the September 2023 cut-off were not available to the EAG. Results on the objective measures of disease burden are reported in Section 2.6.1.4 of the CS, but are not discussed further in this report.

Response rates

In the RAC-RE population (n = 81) an ORR of 74.1% (95% CI: 63.1, 83.2) was observed, including a CR rate of 13.6%. The effectiveness of avapritinib seemed to be better in patients who were treatment naïve (ORR: 90.0%; 95% CI: 73.5, 97.9) compared to those who had received prior therapy (ORR: 64.7%; 95% CI: 50.1, 77.6). ORRs were greater in patients with ASM and SM-AHN (76.9% [95% CI: 46.2, 95.0] and 75.5 [95% CI: 61.7, 86.2] respectively), compared to those with MCL (66.7% [95% CI: 38.4, 88.2]. For the whole population, median duration of response (DOR) had not been reached (not evaluable [NE] [95% CI: 37.1, NE]). Further details on response rates can be found in Table 11 of the CS.

In the PPRE population at the September 2022 data cut-off, the ORR – which was based on pathologic response, rather than the IWG-MRT-ECNM criteria – was [redacted]. In those that responded [redacted], median duration of response was [redacted]; of those who initially responded to treatment, [redacted] were still responding at 24 months (the 24-month DOR rate) These data were provided in response to clarification question A13.[24]

Progression-free survival

At the September 2022 data cut-off, 75.3% of the RAC-RE population (n = 81) data was censored and median PFS had not been reached (NE [95% CI: 39.4, NE months]. The 42-month PFS rate for the whole AdvSM population was 62.9% (95% CI: 41.7, 84.2). The proportion who remained progression-free was greater in patients who were receiving avapritinib as a first-line therapy (24 month PFS: 89.4%; 95% CI: 78.1, 100.0) compared to second or later line of therapy (24 month PFS: 68.8%; 95% CI: 55.5, 82.0). Kaplan Meier (KM) curves for PFS by AdvSM subtype and prior systemic therapy are presented in Figures 10-11 of the CS. Further data on PFS can be found in Table 12 of the CS.

In the PPRE population at the September 2022 data cut-off, [redacted] were alive with no documented progressive disease. However, this value conflicts with the number of patients still alive ([redacted]) at the same data cut-off. Median PFS [redacted] The 24-month PFS KM estimate was [redacted]. The results for this population were provided in response to clarification (question A13).[24]

Overall survival

Overall survival outcomes were only reported for the safety population (n = 105). At the point of data cut-off, median OS had not been reached. The 24-month OS rate was 79.0% (95% CI: 70.8, 87.3). The proportion of patients who were alive at 24 months was greater in those who were receiving avapritinib as a first-line therapy (24-month OS rate: 88.5%; 95% CI: 77.9, 99.1), compared to those

receiving avapritinib as a second or later line of therapy (24 month OS rate: 73.6%; 95% CI: 62.3, 84.9).

At the September 2022 data cut-off, median OS [redacted] in the PPRE population, and the company state that [redacted] patients were still alive. The 24-month OS KM estimate was [redacted]. The results for this population were provided in response to clarification question A13.[24]

Patient-reported outcomes

Patient-reported outcomes are presented in Section B.2.6.1.5 of the CS. The European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire (EORTC-QLQ-C30) patient reported outcome measurements were used to inform the utility estimates in the economic model and are described further below. The AdvSM-SAF TSS and the Patient Global Impression of Symptom Severity (PGIS) assessment were also collected; for details see Sections B.2.6.1.5.2 and Sections B.2.6.1.5.3 of the CS.

The EORTC-QLC-C30 is a five-domain quality of life measure, assessing physical, role, emotional, cognitive and social functioning – as well as calculating an overall global health status score. Mean change in EORTC-QLQ-C30 score from baseline to cycle 17 (68 weeks) is presented for 97 of the 105 patients in the PATHFINDER safety population who received a 200 mg starting dose of avapritinib. The company do not provide a reason why eight of the patients that made up the entire safety cohort (n = 105) were not included in the analysis of the EORTC-QLQ-C30. Overall, there was a mean increase in the global health status score of 20.9 points (standard deviation [SD] 28.5) from baseline to cycle 17 (Table 14, CS). This is above the minimal clinically important difference of 5-10 points described in Musoro et al. (2023).[26] The greatest increases were seen in role functioning (18.0 points [SD 39.4]) and social functioning (18.0 points [SD 37.8]). A decrease of 4.2 points (SD 18.2) in cognitive functioning was observed. Over the seventeen cycles, following the introduction of avapritinib at baseline, mean global health status score improved and remained stable (Figure 14, CS).

Change in EORTC-QLQ-C30 was also presented separately for patients in the safety population receiving avapritinib as 1L and 2L+ therapy. However, the number of patients included in these analyses is not reported in the CS. The mean change in global health status from baseline to cycle 17 was greater for those who were receiving avapritinib as a 1L therapy (23.2 points [SD 30.4]), compared to as a second or later line of therapy (19.5 points [SD 27.7]).

Similar improvements were seen in the PATHFINDER RAC-RE population [redacted], reported in Table 15 of the CS and in Figure 6 and Table 8 of the PATHFINDER clinical summary.[27] The

company do not provide a reason why the other [redacted] patients that make up the entire RAC-RE population (n = 81) were not included in the analysis of the EORTC-QLQ-C30.

3.2.1.4 Safety

Data on AEs are presented in Section B.2.10 of the CS. In the safety population (n = 105), all patients experienced an AE, and 82.9% experienced a Grade 3+ AE. Treatment related AEs (any grade) occurred in 96.2% of patients; while 63.8% of the safety population had a Grade 3+ treatment-related AE.

At the September 2022 data cut-off, the majority of participants had experienced a dose interruption (69.5%) and 77.1% had an AE that led to a dose reduction. Despite the starting dose being 200 mg, the median daily dose of avapritinib was 119.0 mg (range: 29.0, 240.0) in patients who had received prior systemic therapy and 102.5 mg (range: 53.0, 200.0) in patients who had not received prior therapy. The EAG notes that these values are inconsistent with available tablet sizes, but likely reflect calculated average per day dosage, allowing for dose reductions and interruptions.

The most common Grade 3+ treatment emergent AEs (TEAEs) are reported in Table 7. The most common AEs were haematological, including anaemia, thrombocytopenia and neutropenia. Fatal adverse events (Grade 5) occurred in nine patients, none of which were deemed to be related to avapritinib. It is unclear how many patients experienced multiple adverse events, or whether after one adverse event they discontinue treatment or reduce the dose.

Adverse events of special interest (AESIs) included cognitive effects, and intracranial bleeding. Cognitive effects are reported to have occurred in 29 patients (27.6%); 26 of which were related to treatment. Four patients (3.7%) experienced an intracranial bleeding event that was considered to be an AESI. All patients who experienced an intracranial bleeding event discontinued treatment.

At the clarification stage, the EAG asked the company to provide details of the number of patients in the safety and RAC-RE populations who remained on treatment and which dose of avapritinib they were receiving at 12, 24, 36 and 42 months, as well as the median time to treatment discontinuation, and the number of patients who had a permanent or temporary dose reduction. In response, the company stated that they would provide this from the most recent PATHFINDER data cut-off at a ‘later date’. At the date of submission of this report, no details have been provided to the EAG.

Table 7 Number and proportion of patients in PATHFINDER Safety population (n = 105) with Grade 3 or 4 TEAEs at the September 2022 cut-off point. Adapted from Table 25 in the CS

Category	Proportion of safety population [n (%)]
Blood and lymphatic system disorders	**38 (36.2)**
Thrombocytopenia	19 (18.1)
Anaemia	14 (13.3)
Neutropenia	17 (16.2)
Eye disorders	**7 (6.7)**
Periorbital oedema	6 (5.7)
Gastrointestinal disorders	**3 (2.9)**
Diarrhoea	1 (1.0)
General disorders and administration site conditions	6 (5.7)
Oedema peripheral	2 (1.9)
Fatigue	2 (1.9)
Investigations	**24 (22.9)**
Neutrophil count decreased	9 (8.6)
Platelet count decreased	8 (7.6)
White blood cell count decreased	7 (6.7)
Blood bilirubin increased	3 (2.9)
Nervous system disorders	**3 (2.9)**
Cognitive disorder	3 (2.9)
Skin and subcutaneous tissue disorders	**1 (1.0)**

3.2.1.5 Points for critique

PATHFINDER is a single-arm study, and therefore can only provide evidence of how avapritinib affects outcomes in patients from baseline to specific endpoints. The lack of a comparator arm means that there are no within-study estimates of the relative treatment effect of avapritinib against alternative therapies in AdvSM. While the company address this by conducting indirect treatment comparisons, limitations of these (described in Section 3.4.2and 3.4.3) mean there is still considerable uncertainty regarding the relative efficacy of avapritinib against midostaurin, cladribine and BAT.

Although PATHFINDER only enrolled nine patients from the UK, clinical advisors to the EAG consider that the population is broadly representative of patients seen in UK practice. Clinical advisors stated that treatment pathways are similar between the UK, Europe and the United States. However, clinical advice to both the company[28] and the EAG suggested that patients in PATHFINDER were slightly older (median: 68 [range: 39, 88] in safety population [n = 105]) than would be seen in UK practice. Age is a known risk factor for OS: two prognostic scoring systems for AdvSM include age > 60 years as a prognostic factor for OS in patients with AdvSM, although it is unclear how this would affect comparative effectiveness of avapritinib. As a rare condition, there are limited data to indicate whether any differences in certain baseline characteristics would lead to differences in treatment response.

The evidence from PATHFINDER presented in the CS is taken from two data cut-offs: September 2022 (for most results) and April 2021 (for the pooled avapritinib population results, see Section 3.1.5 for further details). During the clarification stage, the company stated that data from the September 2023 data cut-off was available and would be presented at a 'later date'. Given that the median OS has not been reached for the full population, or when stratified by line of therapy, the data presented is immature. Evidence from the later data cut-off would reduce uncertainty around the survival outcomes, and the resulting extrapolations in the economic model (Section 4.2.6.2).

There were minor errors and discrepancies in reporting of results in the CS, including in the reporting of patient disposition. Furthermore, the company did not provide additional PATHFINDER data requested by the EAG at the clarification stage including:

1) the number of patients and specific reasons why each patient was not eligible for the RAC-RE population (question A11b/c);
2) the proportion of patients who remained on treatment receiving each dose of avapritinib at different time points, and the median time to treatment discontinuation (question A16);
3) when dose reductions took place, and the number of patients receiving each dose of avapritinib at a number of time points (question A16); and
4) whether patients on avapritinib permanently reduced their dose or went back to higher dose after the adverse event resolved (question A33).

The company stated in their response that this information would be provided with the updated data cut-off (September 2023) at a 'later date', but at the date of submitting this report, no details have yet been provided to the EAG. This lack of up to date data and analyses also impacts on other aspects of this submission, including the indirect treatment comparisons (Sections 3.4.2and 3.4.3) and the economic evaluation of avapritinib (Section 4.2.6). Since a substantial number of patients experienced an adverse event leading to a dose reduction or dose interruption (see Section 3.2.1.4), the additional information requested on treatment discontinuation and dose reductions would help to ascertain the tolerability and safety of avapritinib and whether there is a relationship between remaining on a higher dose and survival outcomes. The absence of direct or indirect comparisons on the adverse event profile of avapritinib against the comparators (requested in clarification question A30) means there is also uncertainty in the relative tolerability of avapritinib compared to midostaurin, cladribine or BAT in an NHS setting.

3.2.2 EXPLORER

3.2.2.1 Design

The EXPLORER study is used to inform the clinical effectiveness of avapritinib in the indirect treatment comparisons where data from PATHFINDER and EXPLORER are pooled (see Section

3.1.5). This open-label phase I study comprised of two parts: the dose finding phase, and the dose expansion phase to determine the safety and efficacy of avapritinib at the maximum tolerable dose. EXPLORER is described in detail in Appendix M of the CS.

The eligibility criteria for the EXPLORER study were similar to that of PATHFINDER and are described in Appendix M of the CS (Table 2). Briefly, the EXPLORER study included adult patients with ASM, SM-AHN, MCL, a myeloid malignancy or haematologic neoplasm that was relapsed/refractory to standard treatments; for phase 2 (dose expansion phase) patients had to have ASM, SM-AHN or MCL. Patients were enrolled from the United States [redacted] and the UK [redacted].

During the dose finding phase, patients received avapritinib at starting doses ranging from 30 mg to 400 mg. During the dose expansion phase, dose expansion was initially conducted at 300 mg; the 200 mg cohort was subsequently introduced via a protocol amendment, based on longer-term safety, tolerability, and pharmacokinetic data. Results for patients given the 200 mg starting dose are presented separately and are the most relevant for this submission.

3.2.2.2 Patients

Overall, 86 patients were enrolled in the study, of which 69 were diagnosed with AdvSM. Twenty-two AdvSM patients were enrolled onto the dose-finding phase of the study and 47 were included in the dose expansion phase. Only 20 AdvSM patients received avapritinib at a starting dose of 200 mg, of which [redacted] were lost to follow-up. Patient enrolment and disposition is described in Figure 4, Appendix M of the CS.

The demographics of AdvSM patients who received 200mg avapritinib included in the EXPLORER study are reported in the EXPLORER clinical study report (CSR)[29] (January 2023 data cut, Tables 14.1.4.1.2, 14.1.4.2.2 and 14.1.10.1.2). The EXPLORER RAC-RE [redacted] and PATHFINDER RAC-RE (n = 81) populations are broadly similar. In the EXPLORER RAC-RE population, the median age was [redacted], [redacted] of patients were *KIT* D816V positive and [redacted] patients had an ECOG score of 0-1 [redacted]. Overall, [redacted] patients in the EXPLORER RAC-RE population received prior treatments [redacted] than in PATHFINDER RAC-RE population, the proportion of patients in PATHFINDER who had previous exposure to midostaurin (50.6%), was [redacted] EXPLORER ([redacted]).

3.2.2.3 Effectiveness

The company provide details of the EXPLORER study from the April 2022 data cut-off in the CS and Appendix M. Efficacy data for the subgroup of AdvSM patients who received a starting dose of 200 mg avapritinib were not reported in the CS or the appendices. However, the company also provide the EXPLORER CSR for the January 2023 data cut-off, which does provide efficacy data for

the 20 patients who received avapritinib at a starting dose of 200 mg.[29] The results from the January 2023 data cut-off for these patients are described below.

Response rates

In the January 2023 data cut-off, [redacted] patients who received avapritinib at a starting dose of 200 mg from the dose expansion and escalation phase were evaluable per mIWG-MRT-ECNM criteria (RAC-RE population). The ORR (CR + CRh + PR + clinical improvement) in this population was [redacted]. Of these patients, [redacted] achieved a complete remission and [redacted] achieved a complete remission with partial recovery of blood counts (Table 14.2.1.1 of the CSR).[29] Data were not split by AdvSM subgroup for those that received a 200 mg starting dose of avapritinib.

The median duration of response for patients who achieved response and received avapritinib at 200 mg [redacted] was [redacted]. At 30 months, [redacted] of patients still showed a response (the number of patients at risk is [redacted], Table 14.2.2.1 of the CSR).

Progression-free survival

Progression-free survival is reported for patients receiving a starting dose of 200 mg in the EXPLORER CSR (January 2023 data cut-off, Table 14.2.3.3).[29] The median PFS based on the mIWG-MRT-ECNM criteria for all AdvSM patients in the RAC-RE population (n = [redacted]) was [redacted] months (95% CI: [redacted]). The estimated PFS rate at 48 months was [redacted]. PFS data by AdvSM subtype for those receiving 200 mg avapritinib is also presented in the CSR, but the number of patients in each subtype is small.

Overall survival

Overall survival data was available for the safety population, comprised of all 20 patients who received a starting dose of 200 mg avapritinib (January 2023 data cut-off, Table 14.2.4.1 in the CSR).[29] Median OS was [redacted]; and the 54 month OS rate was [redacted]. OS data by AdvSM subtype for those receiving 200 mg avapritinib are also presented in the CSR, but the number of patients in each subtype is small.

Patient-reported outcomes

No patient-reported outcome data were presented for the subgroup of AdvSM patients who received a starting dose of 200 mg avapritinib.

3.2.2.4 Safety

Data on AEs for the total AdvSM population of EXPLORER ([redacted]), who received doses ranging from 30 mg to 400 mg are presented in Appendix M (Section 3.2) of the CS. Treatment-related Grade

≥ 3 AEs were experienced in [redacted] of patients; the most common treatment related adverse events (TRAEs) were [redacted]. Grade ≥ 3 TEAEs experienced by ≥ 1 patient receiving 200 mg starting dose avapritinib (including AdvSM and indolent and smouldering SM patients; [redacted]) are described in Table 8.

Intracranial bleeding was experienced by [redacted] patients overall ([redacted] of whom were treated at the 200 mg starting dose), but [redacted] of these events were associated with pre-existing severe thrombocytopenia. Cognitive effects are reported to have occurred in [redacted] of patients treated at the 200 mg starting dose, but most of these events were Grade ≤ 2.

Table 8 Treatment-related adverse events of Grade ≥ 3 experienced by ≥ 1 patient at 200 mg starting dose (n = 21). From EXPLORER CSR, Table 62

Preferred Term	n (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: TRAE, treatment-related adverse event.

3.2.2.5 Points for critique

The EXPLORER study has more mature data than PATHFINDER, with the median OS being reached. However, the number of AdvSM patients who received a starting dose of 200 mg is small; [redacted] patients in the RAC-RE population and 20 patients in the safety population. This precluded additional analyses by prior lines of therapy or by AdvSM subtype as sample sizes were too small. The EAG considers that pooling the EXPLORER and PATHFINDER studies is a suitable option to provide additional data to reduce some of the uncertainty around the results. However, results from pooling data from the latest 2023 data cuts for both EXPLORER and PATHFINDER were not available. This is discussed in further detail in Section 3.3.

3.2.3 UK Real World Evidence

An open-label CUP cohort of patients in the UK who have received avapritinib is also described in the CS and provides additional efficacy data as well as informing the duration of treatment parameter in the economic model.[17]

Thirteen patients from eleven centres in the UK who received avapritinib were followed up on the CUP. Eleven patients had SM-AHN (84.6%), two were diagnosed with ASM (15.4%), and all patients were *KIT* D816V-positive. The median age was 68.8 years (range 57-76). Ten patients received

avapritinib as a first-line therapy (76.9%), three had received prior midostaurin (n = 1), cladribine (n = 1), or azacytidine (n = 1). Nine patients started avapritinib at a dose of 200 mg once daily.

The ORR, based on the mIWG-ECNM-MRT criteria, was 76.9%, with 7 patients (53.8%) achieving a CR or CR with partial haematologic recovery. As of the last follow-up, two patients with SM-AHN were referred for allo-HSCT. Three patients had died: one from SM progression, one from haematemesis, and one from progression of their associated haematologic neoplasm (a partial response was seen in the SM component).

The CUP cohort also collected data on the safety of avapritinib.[17] Ten patients experienced haematological adverse events, two experienced nausea/vomiting and skin/hair discoloration (grades not reported). Eleven patients required a dose reduction of avapritinib due to haematological toxicity, eight of which remained at a lower dose of 100 mg. Two patients stopped avapritinib owing to disease progression or toxicity.[17] The EAG notes a discrepancy in reporting of the number of patients who had a haematological toxicity (n = 10) and the number who required a dose reduction because of a haematological toxicity (n = 11).[17]

3.2.3.1 Points for critique

The methods describing the CUP cohort of patients receiving avapritinib in the UK is limited and there are no details on the eligibility criteria. This means that it is difficult to determine whether patients eligible for the CUP cohort would be representative of those who would be eligible to receive avapritinib in the NHS.

Access to drugs via CUPs can be limited to those who have already tried alternative therapies.[30] Therefore, it is likely that the included patients in the CUP cohort are selective and not wholly representative of the NHS population who would be eligible for avapritinib, especially as a first-line therapy. Furthermore, the sample size is very small, with only nine patients receiving avapritinib at a starting dose of 200 mg.

3.3 Critique of trials identified and included in the indirect comparisons

Details of the methods used to identify relevant studies for inclusion in the ITC are presented in the CS Section B.2.9 and Appendix D.

Three studies were used to inform the ITC in the CS: a retrospective chart review of best available therapies (BAT) for AdvSM (external control study [ECS])[9] and two phase 2 studies of midostaurin (D2201[18] and A2213[19]) which also informed the midostaurin NICE technology appraisal (TA) 728.[23] The two midostaurin trials were identified from a systematic literature review conducted in January 2021.[31] A systematic literature review was undertaken as part of the CS to identify efficacy and safety

data on treatments in patients with AdvSM; no additional studies were deemed eligible for inclusion in the ITC (see Section 3.1 for further details).

3.3.1 External Control Study (BLU-285-2405)

The ECS conducted by Blueprint Medicines was a multi-centre retrospective chart review. Data were collected on patients with AdvSM who were receiving systemic treatment in participant sites in Europe and the US between 1 January 2009 and 4 October 2021. The EAG's clinical advisors stated that clinical practice in 2009 was similar to now, so results from this study are likely to be generalisable to current practice. No further data cut-offs or updates are available.

The inclusion and exclusion criteria for the ECS were selected to match those of the PATHFINDER and EXPLORER studies. Adult patients who were diagnosed with AdvSM, and who had received at least one line of systemic therapy were included. The endpoints in the ECS included OS (primary endpoint), duration of treatment, change in serum tryptase concentration, time to next line of treatment and safety outcomes. Data on PFS was not available, as this was not recorded in the retrospective real-world cohort. The company also state that where progression was reported, a range of progression criteria were used which were often different to what was used in PATHFINDER. Therefore, no data on this outcome were reported.

From 161 real-world patients who were treated at study sites, 20 were later excluded as data on the key covariate ECOG status were missing. Therefore, 141 patients were included in the analysis population, contributing 222 lines of therapy. The baseline characteristics of the patients included in the ECS and the pooled avapritinib studies are summarised in Table 9. Differences in baseline characteristics between the populations in the ECS and the pooled avapritinib studies are noticeable for region, ECOG status, AdvSM subtype, proportion of patients with thrombocytopenia, serum tryptase levels, number of mutated genes, and proportion of patients with prior exposure to antineoplastic therapy.

Table 9 Baseline characteristics for External Control Study. Source: Adapted from Reiter et al., 2022[9] and Table 17, CS

	External Control Study			**Pooled PATHFINDER and EXPLORER (safety)**
	Total Population[a]	**Midostaurin[a]**	**Cladribine[a]**	**Avapritinib**
N patients	141	94	44	176
N unique LOT	222	99	49	176
Age, median years (range)	67.8 (21, 88)	69.1 (26, 87)	66.1 (45, 88)	68.0 (31, 88)
Female, n (%)	76 (34%)	32 (32%)	20 (41%)	73 (42%)
Region				
North America	34 (15%)	19 (19%)	3 (6%)	102 (58%)
Europe	188 (85%)	80 (81%)	46 (94%)	74 (42%)
ECOG Status				

	External Control Study			Pooled PATHFINDER and EXPLORER (safety)
	Total Population[a]	**Midostaurin[a]**	**Cladribine[a]**	**Avapritinib**
ECOG status - 0	50 (23%)	19 (19%)	3 (6%)	36 (21%)
ECOG status - 1	129 (58%)	54 (55%)	35 (71%)	92 (52%)
ECOG status ≥ 2	43 (19%)	26 (26%)	5 (10%)	48 (27%)
AdvSM subtype, n (%)				
ASM	68 (31%)	21 (21%)	17 (35%)	29 (17%)
SM-AHN	121 (55%)	65 (66%)	25 (51%)	119 (68%)
MCL	33 (15%)	13 (13%)	7 (14%)	28 (16%)
Thrombocytopenia	120 (54%)	56 (58%)	32 (65%)	67 (38%)
Number tested for *KIT* mutation	140 (99%)	93 (99%)	43 (98%)	170 (97%)
KIT D816V, n (%)	128 (91%)	83 (89%)	39 (91%)	156 (92%)
Serum tryptase level ≥125ng/mL, n (%)	144 (65%)	68 (69%)	32 (65%)	132 (75%)
Number tested for SRSF2/ ASXL1/ RUNX1 gene panel	107 (75.9%)	78 (83%)	40 (91%)	176 (100%)
0 mutated genes	41 (38%)	27 (35%)	15 (38%)	92 (52%)
1 mutated gene	44 (41%)	34 (44%)	15 (38%)	54 (31%)
>2 mutated genes	22 (21%)	17 (22%)	10 (25%)	30 (17%)
Prior systemic therapy				
Any prior antineoplastic therapy, n (%)	104 (47%)	41 (41%)	29 (59%)	110 (63%)
Midostaurin	99 (51%)[b]	5 (5%)	20 (41%)	81 (46%)
Cladribine	20 (19%)[b]	23 (23%)	5 (10%)	22 (13%)
Interferon alpha	11 (6%)[b]	7 (7%)	8 (16%)	14 (8%)
Hydroxycarbamide	17 (9%)[b]	7 (7%)	6 (12%)	9 (5%)
Imatinib	2 (1%)[b]	5 (5%)	2 (4.1%)	10 (6%)
Dasatinib	2 (1%)[b]	5 (4%)	2 (4.1%)	6 (3%)
Peg-interferon alpha	8 (4%)[b]	4 (4%)	2 (4.1%)	3 (2%)
Brentuximab vedotin	4 (2%)[b]			

[a] Data is presented for the 222 unique lines of therapy rather than based on the number of patients. Proportions may not add up owing to rounding; [b]Agent level information was only available for 196 unique lines of therapy.

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; LOT, line of therapy; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with associated haematological neoplasm.

3.3.1.1 Points for critique

The eligibility criteria for the ECS were chosen to be in-line with PATHFINDER and EXPLORER. While this allows for greater comparability between the studies and real-world evidence, there is uncertainty as to whether the ECS population is representative of patients seen in NHS clinical practice. The company do not provide details of patients excluded due to these eligibility criteria.

Patient characteristics are only reported for those who were treated with midostaurin or cladribine in the ECS. Where details for the total population of the ECS are reported,[9] patient characteristics are provided by unique lines of therapy (n = 222), rather than individual patients (n = 141). This means

that a comparison with the PATHFINDER and EXPLORER studies – which present data for individual patients, despite some of them having had prior therapy – is difficult, especially in the BAT cohort, where around 35% of the data presented is double (or perhaps more) counted.

The company were unable to collect data on PFS in the ECS. PFS was considered to be an important outcome in the NICE scope so there is substantial uncertainty in the relative efficacy of avapritinib compared to midostaurin for this outcome (although exploratory analyses of PFS were conducted in the MAIC), cladribine and BAT.

3.3.2 Midostaurin studies: A2213 and D2201

The two midostaurin studies (D2201[18] and A2213[19]) are phase 2, open-label, single-arm multicentre studies of midostaurin, given orally at 100 mg twice daily as continuous four-week cycles.

Key eligibility criteria for the midostaurin studies are similar to EXPLORER and PATHFINDER in terms of age, disease subgroups and ECOG performance status. The primary endpoint in these studies was best overall response/ORR (measured by the Valent criteria); secondary endpoints included OS, PFS, DOR, for both studies, as well as HRQoL in D2201 and pharmacokinetics in A2213. Two analysis populations were considered: the full-analysis set (FAS) which included all patients who had midostaurin assigned according to the intention to treat principle (all of whom went on to receive ≥ 1 dose of midostaurin); and the primary efficacy population (PEP) which included all patients who had measurable (and in the case of A2213, non-measurable) C-findings. The FAS is equivalent to the safety population and the PEP is equivalent to the RAC-RE population in the avapritinib studies.[23]

Across both studies, 142 patients with AdvSM were included in the full-analysis set (116 patients in D2201 and 26 in A2213), and 115 were included in the primary-efficacy population (89 in D2201 and 26 in A2213).[23] Baseline characteristics of the patients included in the midostaurin studies and avapritinib studies are summarised in Table 10.

The populations in the midostaurin studies compared to the avapritinib studies are relatively similar with regards to age, sex, and bone marrow mast cell burden. There are differences in other baseline characteristics however, ECOG status (in the A2213 study), the proportion of patients who had received prior lines of treatment, *KIT* D816V mutation status and the number of C-findings (although these were reported differently in the avapritinib and midostaurin studies).

Table 10 Baseline characteristics of patients included in the midostaurin and avapritinib studies from 2021 data cut-off. Source: MAIC report

Study	EXPLORER - Avapritinib[a]		PATHFINDER - Avapritinib[b]		A2213 - Midostaurin	D2201 - Midostaurin	
Population	[redacted]	[redacted]	[redacted]	[redacted]	FAS = PEP (N = 26)	PEP (N = 89)	FAS (N = 116)
Age (years), median (range)	[redacted]	[redacted]	[redacted]	[redacted]	64.5 (24, 79)	64 (25, 82)	63.0 (25, 82)
Sex, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	15 (58)	57 (64)	76 (66)
Female	[redacted]	[redacted]	[redacted]	[redacted]	11 (42)	32 (36)	40 (34)
Race, n (%)							
White	[redacted]	[redacted]	[redacted]	[redacted]	21 (81)	86 (97)	111 (96)
Non-White	[redacted]	[redacted]	[redacted]	[redacted]	NR (NR)	2 (2)	3 (3)
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	NR (NR)	1 (1)	2 (2)
ECOG performance status, n (%)							
0	[redacted]	[redacted]	[redacted]	[redacted]	12 (46)	57 (64)	77 (66)
1	[redacted]	[redacted]	[redacted]	[redacted]			
2	[redacted]	[redacted]	[redacted]	[redacted]	14 (54)	32 (36)	39 (34)
3	[redacted]	[redacted]	[redacted]	[redacted]			
No. of previous therapies, n (%)							
0	[redacted]	[redacted]	[redacted]	[redacted]	5 (19)	52 (58)	64 (55)
1					8 (31)	21 (24)	29 (25)
2	[redacted]	[redacted]	[redacted]	[redacted]	6 (23)	12 (13)	15 (13)
≥ 3					7 (27)	4 (4)	8 (7)
Subtype of AdvSM, n (%)							
ASM	[redacted]	[redacted]	[redacted]	[redacted]	3 (12)	16 (18)	22 (19)
SM-ANH	[redacted]	[redacted]	[redacted]	[redacted]	17 (65)	57 (64)	73 (63)
MCL	[redacted]	[redacted]	[redacted]	[redacted]	6 (23)	16 (18)	21 (18)
***KIT* D816V mutation status, n (%)**							
Positive	[redacted]	[redacted]	[redacted]	[redacted]	20 (77)	77 (87)	98 (84)
Negative	[redacted]	[redacted]	[redacted]	[redacted]	5 (19)	10 (11)	13 (11)
Other	[redacted]	[redacted]	[redacted]	[redacted]	1 (4)	2 (2)	5 (4)
Bone marrow mast cell burden (%), median (range)	[redacted]	[redacted]	[redacted]	[redacted]	50 (5, 95)	50 (8, 98)	40 (3, 98)
Serum tryptase level (µg/L), median (range)	[redacted]	[redacted]	[redacted]	[redacted]	323 (22, 1255)	236 (27, 12069)	200 (2, 12069)
Number of C-findings per patient, n (%)							
0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
1	[redacted]	[redacted]	[redacted]	[redacted]	3 (12)	31 (35)	31 (27)
2	[redacted]	[redacted]	[redacted]	[redacted]	10 (38)	20 (22)	20 (17)

≥ 3	[redacted]		[redacted]		[redacted]		13 (50)	38 (43)	38 (33)

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; MCL, mast cell leukaemia; NR, not reported; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated haematological neoplasm.

[a]The EXPLORER population include patients who received any dose of avapritinib including doses between 30-400mg: 17 and 20 patients in RAC-RE and safety cohort received 200 mg avapritinib respectively. [b]The PATHFINDER safety population in this table includes 2 patients who did not receive a starting dose of 200mg.

3.3.2.1 Points for critique

The two included studies of midostaurin are relevant for this appraisal. Although the company did not conduct a quality assessment of these studies, they have been previously evaluated in TA728.[23] The EAG for TA728 deemed the studies to be well reported but noted that confounding variables are not described or adjusted for in the analyses.

As discussed above, there are differences between the midostaurin and avapritinib populations. The company acknowledge the differences between the study populations and conduct adjustments prior to the analysis of the relative efficacy of avapritinib compared to midostaurin (see Section 3.4).

The dose of midostaurin in the D2201 and A2213 studies is reflective of that recommended by NICE for use in the NHS (100 mg twice daily).

3.4 Critique of the indirect comparisons

The company report details of the indirect treatment comparisons in the CS Document B, CS Appendix M, the ECS CSR, in two published papers,[9, 32] and a MAIC report provided by the company in response to the clarification questions.[31] Clinical evidence on avapritinib in patients with AdvSM was informed by the two avapritinib single-arm studies (PATHFINDER and EXPLORER). Therefore, unanchored indirect treatment comparisons were conducted to provide comparative evidence of avapritinib against midostaurin and off label therapies (labelled BAT). These include:

- IPTW analysis using the ECS (BLU-285-2405) which includes real-world data on BAT including midostaurin and cladribine. This uses **individual participant data** for both the avapritinib and comparator arms.
- Unanchored MAIC analysis using **individual participant data** from the PATHFINDER and EXPLORER studies, alongside **aggregate data** from the two phase 2 studies of midostaurin in patients with AdvSM (D2201 and A2213).

A summary of the indirect treatment comparisons conducted by the company is presented in Table 11. The IPTW using the PATHFINDER data (September 2022 data cut-off) and ECS was used to inform the company's base-case analysis in the economic model. The MAIC using the pooled populations of PATHFINDER and EXPLORER from the 2020 data cut-offs (as described in Pilkington et al., 2022[32]) was used in a scenario analysis to model the use of allo-HSCT as a potential curative option for patients with AdvSM.

Table 11 Summary of the populations used in the indirect treatment comparisons. Source: CS, Tables 19-21 and MAIC report[31]

Data set	Analysis Population	Dose	Lines	Outcomes	EAG notes
Inverse Propensity Score Weighting					
Avapritinib					The results are only presented for OS in this population in the CS. At clarification stage, the EAG requested this analysis to be updated with the latest data cuts. However, this was not provided. **The populations highlighted in bold represent those that were used to inform the economic evaluation.**
EXPLORER and PATHFINDER pooled population (April 2021)	Safety	All doses	All lines	OS (N = 176)	
PATHFINDER (September 2022)	**Safety**	**200 mg**	**1L**	**OS; DOT (N = 38)**	
			2L+	**OS; DOT (N = 67)**	
	RAC-RE	200 mg	1L	**OS (N = 30)**	
			2L+	OS (N = 51)	
Comparator					
External control study	**Midostaurin**	**-**	**All lines**	**OS; DOT (N = 94 [99 LOT])**	
		-	**1L**	**OS; DOT (N = 58 [58 LOT])**	
	Cladribine	**-**	**All lines**	**OS; DOT (N = 44 [49])**	
		-	**2L+**	**OS (N = 27 [29 LOT]); DOT (N= 24 [25 LOT])**	
	BAT	**-**	**2L+**	**OS (N = 73 [104 LOT]); DOT (N = 67 [97 LOT])**	
Matching Adjusted Indirect Comparison					
Avapritinib					At clarification stage, the EAG requested this analysis to be updated with the most recent data cut-off from PATHFINDER and EXPLORER (both 2023). However, this was not provided.
EXPLORER and PATHFINDER pooled population (May/June 2020)	RAC-RE	All doses	MIDO naïve	CR + ORR (N = 46) – used in Allo-HSCT scenario analysis only.	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Data set	Analysis Population	Dose	Lines	Outcomes	EAG notes
			[redacted]	[redacted]	
		[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	
Midostaurin					
D2201 and A2213 pooled population	PEP		All lines	OS (N = 115)	
	PEP (SM-AHN)		All lines	OS (N = 74)	
	FAS		All lines	OS (N = 142)	
D2201	PEP		All lines	PFS, CR, ORR, CR (N = 89)	
	PEP (SM-AHN)		All lines	OS, ORR (N = 57)	

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; BAT, best available therapy; CR, complete response; CS, company submission; DOT, duration of treatment; EAG, External Assessment Group; FAS, full-analysis set; LOT, line of therapy; MIDO, midostaurin; ORR, overall response rate; OS, overall survival; PEP, primary efficacy population; PFS, progression-free survival; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated haematological neoplasm.

3.4.1 Selection of covariates

The selection of covariates for adjustment in the indirect treatment comparison is described in the CS Appendix D, with further details being provided at the clarification stage. Covariates were selected *a priori* and were informed through clinical input, existing literature or univariate Cox regression analyses of the PATHFINDER data (for the MAIC). Many of the covariates coincide with components of the mutation-adjusted risk score (MARS) and the international prognostic scoring system for mastocytosis (IPSM).[33, 34] Covariates that were adjusted in the IPTW and the MAIC are described in Table 12. Clinical advisors to the EAG considered age, ECOG status, AdvSM subtype, serum tryptase level, prior systemic therapy, *KIT* D816V mutation status, bone marrow mast cell burden and number of C-findings to be the most important prognostic factors or treatment effect modifiers (italicised in Table 12). Furthermore, the EAG clinical advisors suggested that recently, mutational status (such as SRSF2) has been deemed as an important risk factor in AdvSM, and can influence how the disease progresses and the patient's prognosis.

For some of the ITC analyses, the company pool the results from the EXPLORER and PATHFINDER studies (from the April 2021 data cut-off) who received avapritinib at any dose (n = 176). At the clarification stage, the EAG asked the company to provide an updated efficacy analysis using the pooled avapritinib population at the latest data cut-off. However, this was not provided although the company noted this would be provided at a 'later date'.

Table 12 Covariates considered in IPTW and MAIC adjustments. Adapted from clarification response, Table 7

Variable	Which analysis was it adjusted in?	Rationale for Inclusion as Covariate by Company
Age (years)	*IPTW, MAIC*	*MARS and IPSM prognostic scores*
Sex (male/female)	IPTW	Expert opinion and published literature
Race (white/non-white)	MAIC	Cox regression analyses of PATHFINDER data
Region (North America/Europe)	IPTW	Expert opinion – differences in treatment availability and practice
ECOG Score (0, 1, 2)	*IPTW, MAIC**	*Expert opinion, Cox regression analyses of PATHFINDER data*
Proportion with anaemia (%)	IPTW	Component of MARS prognostic score
Proportion with thrombocytopenia (%)	*IPTW*	*Component of MARS prognostic score*
AdvSM subtype (SM-AHN, ASM or MCL)	*IPTW, MAIC*	*Expert opinion and published literature, Cox regression analyses of PATHFINDER data*
Any skin involvement (n [%])	IPTW	Component of IPSM prognostic score
Leukocyte count ≥16 × 10^9/L, (n [%])	IPTW	Component of IPSM prognostic score
Serum tryptase ≥125ng/mL (n [%])	*IPTW*	*Component of IPSM prognostic score*
SRSF2/ASXL1/RUNX1 mutation (n [%])	IPTW	Component of MARS prognostic score

Variable	Which analysis was it adjusted in?	Rationale for Inclusion as Covariate by Company
Number of mutated genes in S/A/R panel (n [%])	IPTW	Component of MARS prognostic score
Prior systemic therapy – number of prior lines	*IPTW, MAIC**	*Expert opinion, Cox regression analyses of PATHFINDER data*
Types of prior systemic therapy	*IPTW, MAIC**	*Expert opinion, Cox regression analyses of PATHFINDER data*
KIT D816V mutation status	*MAIC**	*Cox regression analyses of PATHFINDER data*
Bone marrow mast cell burden	*MAIC**	*Cox regression analyses of PATHFINDER data*
Presence of C-findings[a]	*MAIC**	*Cox regression analyses of PATHFINDER data*

NB. Rows in italics denote covariates deemed as important prognostic factors and treatment effect modifiers by EAG clinical advisors. *These variables were only adjusted in the MAICs of overall response rate and complete response rate. [a]Presence of C-findings was only adjusted for in sensitivity analyses as part of the MAICs. Described in detail in Section 3.4.3.1.

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPSM, international prognostic scoring system for mastocytosis; IPTW, inverse probability of treatment weighting; MAIC, matching adjusted indirect comparison; MARS, mutation-adjusted risk score; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with associated haematological neoplasms.

3.4.2 Inverse Probability Treatment Weighting

IPTW-weighted Cox proportional hazard models were used to evaluate the relative clinical effectiveness of avapritinib versus midostaurin, cladribine and BAT. Methods and results are described in Section B.2.9.2 of the CS. Several analyses were conducted, and these are summarised in Table 11.

3.4.2.1 Population adjustment method

The IPTW approach was used to weight the populations from pooled PATHFINDER and EXPLORER studies, and the PATHFINDER study alone; with the ECS to reduce imbalances in the baseline characteristics across the populations. Using doubly robust methods, the company first adjusted for the baseline variables through propensity score modelling. Based on the propensity score, for each LOT in the analysis (rather than for each patient), stabilised inverse probability of treatment weights were calculated using a logistic regression model. Further adjustment was then made for key covariates that remained unbalanced after weighting.

The EAG requested additional information regarding results from the IPTW at the clarification stage, including odds ratios from the logistic regression analyses used in the doubly robust estimation, the propensity score distributions between the intervention/comparator arms before/after treatment weighting and a distribution of weights applied in each IPTW analysis, as per the NICE TSD 18 guidance. In their response the company stated that they would provide this using the most recent

PATHFINDER data-cut off at a later date. However, this has not been provided at the time of writing this report.

The company present baseline characteristics before and after adjustment for each analysis population in Appendix M, except for the pooled PATHFINDER and EXPLORER (April 2021 data cut-off) population compared to midostaurin and cladribine which was not presented.

In the analysis comparing avapritinib and midostaurin at first line, the IPTW adjustment resulted in improved standardised differences to less than 10% (considered indicative of meaningful imbalances between the two cohorts) between populations for nine of the sixteen patient characteristics. This included seven of the nine variables deemed to be key prognostic indicators in AdvSM according to clinical advice to the EAG. After adjustment, differences in ECOG status remained for those who had an ECOG score of 1 or ≥ 2. The effective sample size after adjustment (N = 37 for avapritinib, and 59 for midostaurin) remained similar to the total population included in the analysis prior to adjustment.

At second line or later, the IPTW adjustment of avapritinib and cladribine resulted in improved standardised differences to less than 10% between populations for eight of the 21 patient characteristics, including four of the nine variables deemed to be key prognostic indicators in AdvSM according to clinical advice to the EAG. After adjustment, differences in the key prognostic indicators (according to clinical advice to the EAG) remained for ECOG status, age, AdvSM subtype and serum tryptase concentration. Adjustment resulted in the effective sample size increasing for the avapritinib population (N = 74, compared to 67 prior to adjustment), while the cladribine population was reduced following adjustment (Effective N = 22 (23 LOT), compared to 27 (29 LOT) prior to adjustment). When comparing avapritinib and BAT at second line or later, population adjustment improved standardised differences to less than 10% between populations in 13 of 21 patient characteristics, including four of the nine characteristics deemed to be key prognostic variables in AdvSM by the EAG's clinical advisors. Differences in the key prognostic indicators (according to EAG's clinical advisors) remained in ECOG status, age, presence of thrombocytopenia, serum tryptase concentration and proportion of patients with SM-AHN. Following adjustment, the effective sample size for the avapritinib population remained the same, while the sample size for BAT reduced from 73 patients (104 LOT) to an effective sample size of 67 patients (96 LOT).

The mean stabilized weights from the IPTW for OS and DOR were similar between analyses, and ranged from [redacted] in the analyses presented in the ECS CSR. The range of weights for all analyses was between [redacted]. The EAG asked the company to provide the distribution of weights for the analyses presented in the CS at the clarification stage, but this was not provided.

3.4.2.2 Results

Results from the IPTW are presented in Sections B.2.9.2.4 and B.2.9.2.5 of the CS. The results presented in the EAR will focus on the analyses used in the company and EAG base cases in the economic model. This includes analysis of the PATHFINDER safety population at the September 2022 data cut-off, compared to patients receiving midostaurin at first-line, and cladribine or BAT at second line or later.

Overall survival

Results from the IPTW of OS comparing avapritinib (PATHFINDER safety population, September 2022 data cut) and midostaurin, cladribine and BAT (from the ECS) are presented in Table 20 and Figures 20, 21 and 22 of the CS. The pooled PATHFINDER/EXPLORER analysis is not presented in the CS as it included all doses of avapritinib and is therefore not considered relevant. At first line, avapritinib was associated with significantly improved overall survival compared to midostaurin (HR [95% CI]: [redacted]). At second line, avapritinib was also associated with improvements in overall survival compared to cladribine (HR [95% CI]: [redacted]) and BAT (HR [95% CI]: [redacted]).

Duration of treatment

In the absence of PFS data in the ECS (Section 3.3.1.1), the company conducted an IPTW analysis of duration of treatment (DOT). In the company's base-case analysis in the economic model, the company consider that PFS is assumed to be the same as DOT and that treatments would be administered until progression, which was deemed to be reasonable by the company's UK clinical expert. This IPTW compared avapritinib (PATHFINDER safety population, September 2022 data cut) and midostaurin, cladribine and BAT (from the ECS), presented in Table 21 of the CS. At first line, avapritinib was associated with a significantly longer DOT compared to midostaurin (HR [95% CI]: [redacted]). At second line or later avapritinib showed a greater DOT compared to cladribine (HR [95% CI]: [redacted]) and BAT (HR [95% CI]: [redacted].

3.4.2.3 Points for critique

The EAG's main critique with the IPTW analyses is that they are based on an old data cut-off, and therefore are not providing the most up-to-date evidence on the efficacy of avapritinib compared to midostaurin, cladribine and BAT (from 2021 in the pooled analyses with all doses, and 2022 for analyses using PATHFINDER and 200 mg dose only). At the clarification stage, the EAG requested updated IPTW analyses using the most recent data cut-offs (question A19). In response, the company said that this would be provided at a 'later date'.

The EAG were presented with insufficient details of the methods and results from the population adjustment methods used in the IPTW, meaning it has been difficult to determine whether the analyses were appropriately conducted. The company stated that the details requested in clarification question A20, would be provided at a 'later date', but these were not received at the time of writing this report. It is therefore difficult to determine how well the populations have been matched following adjustment, and the extent to which particular participant characteristics are over/under-represented based on the distribution of weights in the analysis.

Alongside this, the EAG have concerns over the choice of variables chosen for adjustment in the analysis. Clinical advisers considered that *KIT* D816V mutation status, bone marrow mast cell burden and presence of C-findings were key prognostic variables in AdvSM, which were not adjusted for in the IPTW, and therefore may bias the IPTW analysis. The EAG asked the company to explain the potential impact of not adjusting for these variables in clarification question A18. The company stated, and the EAG accept, that bone marrow mast cell burden and C-findings may not have been collected in routine practice, and therefore were not available for use within the ECS. The company also argued that prognostic scoring systems have found no evidence of *KIT* D861V mutation status and mast cell burden to be associated with OS. However, this contrasts with the choice of variables used in the MAIC, whereby *KIT* D816V and mast cell burden were adjusted for in analyses of CR and ORR, as mutation status was deemed to be a 'potential prognostic' factor according to univariate logistic regression analysis of PATHFINDER data. The company do not discuss the prognostic impact of C-findings, but similarly, it was deemed a 'potential prognostic' factor in the logistic and Cox regression models used to determine variables for adjustment in the MAIC analysis. Given that several key prognostic factors were not adjusted for in the IPTW, the EAG does not consider that the company's analysis meets one of the key assumptions in propensity score methods, namely that there are no unmeasured confounders.[35]

The EAG also consider that some of the variables included in the adjustment may have been unnecessary and could have led to an over-adjustment. Particularly variables such as 'region' where there were large differences between the populations before and after weighting. Clinical advice to the EAG suggested that the treatment and care for AdvSM is similar in Europe and North America. This is also reflected in the CS Section B.2.9.2.3.1, where the company suggest that the standards of care are similar and will, therefore, not introduce undue bias. Therefore, while the EAG acknowledge the differences between the proportion of the population treated in these regions in the avapritinib studies compared to ECS – thus region being linked to treatment assignment – it should not have been a priority for adjustment, since it is not expected to influence outcomes.[36] The inclusion of variables such as region could reduce the effective sample sizes in the avapritinib and comparator populations and increase uncertainty in the results.

3.4.3 Matching Adjusted Indirect Comparisons (MAIC)

The company also conducted an unanchored MAIC to evaluate the relative clinical effectiveness of avapritinib versus midostaurin (see Section 3.3.2 for a description of the trials). The company do not use the MAIC in the base case economic model, however they state that the MAIC provides additional comparative evidence for ORR, CR and OS, and informs a scenario analysis in the economic model. Methods and results are described in Section B.2.9.3 and Appendix D of the CS. Additional MAIC analyses are reported in Pilkington et al., 2022[32] and a full report on the MAIC submitted by the company in response to clarifications.[31] In order to identify the studies for inclusion in the MAIC, a SLR was conducted in January 2021, and from 3,001 studies identified during database searching, four studies, including the two midostaurin studies and the two avapritinib studies, were eligible for inclusion in the MAIC.

For some of the MAIC analyses, the avapritinib studies were pooled together to form the avapritinib arm, and the midostaurin studies were pooled together to form a midostaurin arm to which the avapritinib arm was compared. In Appendix D, the company argue that this was appropriate to conserve sample size and, therefore, reduce uncertainty. Methods of pooling of the avapritinib populations are described above (Section 3.3). At the clarification stage, the company were asked to provide details of their methods of pooling the midostaurin populations. The company confirmed that for response outcomes of ORR and CR, naïve pooling (adding numerators and denominators together) was used; and for OS outcomes, KM curves for the midostaurin studies were digitised to create pseudo-patient-level data, which was (naïvely) pooled for analysis. Baseline characteristics were combined using weighted averages. For other analyses, only the D2201 midostaurin population is used in the MAIC of ORR and CR, as a post-hoc analysis of this study provided responses based on the IWG-MRT-ECNM criteria.[37]

The MAIC report provided by the company also included additional analyses not described in the CS. This included exploratory analyses of PFS comparing avapritinib and midostaurin (described in Section 3.4.3.2, and a separate MAIC of avapritinib compared to BAT (not described in this report).

3.4.3.1 Population adjustment

A number of variables were adjusted for, chosen based on exploratory subgroup analyses of the avapritinib patient-level data. Univariate Cox proportional hazards and logistic regression analyses to explore the impact of patient characteristics on OS and PFS, and ORR and CR respectively were conducted. These were presented in the MAIC report for the pooled EXPLORER and PATHFINDER populations for a 2020 and 2021 data cut off.[31] Patient characteristics were deemed to be potentially prognostic if the p-value was < 0.1, based on the 2020 data cut off. Not all the potentially prognostic factors were adjusted for as only some were reported in the comparator evidence.

The patient characteristics that were adjusted for include age, AdvSM subtype and race were in analyses of OS and PFS; for analysis of ORR and CR, ECOG performance status, prior systemic therapy, *KIT* D816V mutation status and bone marrow mast cell burden were also adjusted for. The number of C-findings was also deemed a potential prognostic factor, but in response to clarification questions, the company stated that the lack of comparability in the definition meant that it was deemed 'too problematic', so was not used in adjustment. This contradicts what is mentioned in the MAIC report, which stated that C-findings were used for adjustment in some of the sensitivity analyses to assess the impact of matching on the number of C-findings.[31]

Additional details of adjustment were provided in the MAIC report in response to the EAG's clarification questions. The baseline characteristics before and after adjustment, and the distribution of weights for the analyses presented are summarised in Table 13.

Table 13 Summary of baseline characteristics before and after matching for OS, PFS, ORR and CR for the analyses described in Section 3.4.3.2. Source: MAIC report, Tables 34 and 46[31]

	OS and PFS (200mg population)			ORR and CR (200mg population)		
	AVA (Pooled)	Weighted AVA (Pooled)	MIDO (Pooled)	AVA (Pooled)	Weighted AVA (Pooled)	MIDO (D2201)
N/ESS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age ≤ median in MIDO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SM-AHN subtype (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASM subtype (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCL subtype (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (white %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 0/1 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KIT D816 Positive (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow mast cell ≤ median in MIDO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASM, aggressive systemic mastocytosis; AVA, avapritinib; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; MCL, mast cell leukaemia; MIDO, midostaurin; ORR, overall response rate; PFS, progression-free survival; SM-AHN, systemic mastocytosis with associated haematological neoplasm.

3.4.3.2 Results

Results of the MAIC are presented in Section B.2.9.3.3 of the CS from the 2020 data cut-off (Pilkington et al., 2022[32]). The full report on the MAIC submitted by the company in response to clarification questions provided updated MAIC analysis from 2021 data cut-offs – which are reported below.[31]

Overall survival

Patients treated with avapritinib in the EXPLORER and PATHFINDER pooled RAC-RE population (all lines, 200 mg), had improved overall survival compared to patients treated with midostaurin (pooled population, all lines) with a HR of [redacted]. The effective sample size (ESS) for the avapritinib population reduced to [redacted].

Progression-free survival

In the MAIC report, the company conduct exploratory MAIC analyses comparing PFS from the avapritinib and midostaurin trials. The company state that PFS is unlikely to be comparable owing to different definitions of response across the two studies, so the ITCs should be interpreted with caution. Only the D2201 midostaurin population is used in this MAIC, as a post-hoc analysis on this population was conducted to update responses to be based on the IWG-MRT-ECNM criteria.[37]

The MAIC shows that PFS for avapritinib (pooled RAC-RE population, all lines, 200 mg dose) was superior compared to midostaurin (D2201 PEP population) with a HR of [redacted]. The ESS was [redacted].

Overall response rate and complete remission

Patients treated with avapritinib (pooled RAC-RE population, all lines, 200 mg dose) were more likely to achieve an overall response compared to patients treated with midostaurin (D2201 PEP population, all lines) with an odds ratio (OR) of [redacted].

The MAIC comparing complete remission between avapritinib and midostaurin is very uncertain due to small numbers of patients achieving a complete remission as per the IWG-MRT-ECNM criteria (1 in the D2201 trial, [redacted] in the pooled PATHFINDER and EXPLORER trials).

The effective sample size in both of the response-rate based analyses [redacted] was more than half that of the unweighted sample size [redacted]. This is likely to be due to an increase in the number of variables adjusted for.

3.4.3.3 Points for critique

The EAG's main critique of the MAIC analyses is that they are based on an old data cut-off (2021), and therefore are not providing the most up-to-date evidence on the efficacy of avapritinib compared to midostaurin. At the clarification stage, the EAG requested updated MAIC analyses using the most recent data cut-offs (question A26). In response, the company said that this would be provided at a 'later date'.

In the absence of detailed methodology and results for the population adjustments in the IPTW, the MAIC provides additional evidence on the clinical effectiveness of avapritinib compared to

midostaurin. While the EAG would usually consider IPTW to provide the most robust evidence in ITCs, the lack of detail and transparency in the reporting of it has meant that the MAIC – which has a comprehensive report, and provides evidence on the relative efficacy of avapritinib compared to midostaurin on PFS – may play an important role in providing evidence for the relative efficacy of avapritinib.

Despite this, the company do not present any analyses relevant to this decision problem (i.e. 200 mg avapritinib) in either the IPTW or MAIC that can be compared, making it difficult for the EAG to determine whether the findings in the different ITCs were consistent. In addition, no MAIC analyses were conducted comparing avapritinib and midostaurin as a first-line therapy. Given that midostaurin is the main comparator at first-line therapy, this analysis could have provided valuable evidence of the efficacy of avapritinib at this position in the treatment pathway, especially given the uncertainties with the IPTW analyses (detailed in Section 3.4.2.3).

While the MAIC report supplied by the company after the clarification stage provided detailed information on the population matching, the EAG has some concerns about the variables chosen for adjustment. Patient characteristics that were adjusted for were identified through univariate regression analyses of the PATHFINDER data using the 2020 data cut-off. A p-value of 0.1 was chosen as an arbitrary cut-off to indicate potentially prognostic variables. When repeating the analyses using the 2021 data cut-off however, some of the variables identified as potentially prognostic no longer met the criteria (i.e. the p-value was > 0.1), yet they were still used in adjustments. It is unclear why these variables were then adjusted for, given the pre-defined criteria. The number of C-findings was a consistent prognostic factor in the PATHFINDER univariate regression analyses but given differences in the measurement of these between the studies, this variable was only adjusted for in a sensitivity analysis of the main endpoint (OS) and population of interest (pooled avapritinib RAC-RE population, all doses and all lines). When it was adjusted for, the HR for OS increased, reducing the relative efficacy of avapritinib on OS (without adjustment of C-findings, HR: [redacted]; with adjustment of C-findings, [redacted] – from Table 16 of the MAIC report).

The choice of variables for adjustment also has an impact on the effective sample size for the MAIC analyses of ORR and CR. Seven variables were adjusted for in these analyses, which led to a substantial reduction in the ESS for avapritinib. This highlights the differences in the baseline characteristics between populations, leading to a substantial number of patients being down weighted in the analyses, increasing the uncertainty of the results.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness section

The evidence presented in the CS on the efficacy and safety of avapritinib for treating AdvSM is primarily based on the results of the ongoing uncontrolled PATHFINDER study. Data were presented from the September 2022 cut-off; at the clarification stage the company stated that an additional data cut-off was available (September 2023) and would be provided "at a later date", however, no updated analyses have been provided. Therefore, the clinical effectiveness evidence is severely limited in terms of study design and data maturity.

In the absence of direct within-trial evidence, two ITCs were conducted to estimate the relative effects of avapritinib compared to midostaurin, cladribine and BAT. The analyses comparing avapritinib versus BAT are not likely to be representative of NHS practice, as the BAT arm contains a substantial proportion of patients ([redacted] who received midostaurin as a second line therapy.

The IPTW analysis using PATHFINDER and the ECS is used to inform the base-case economic model (although analyses using a pooled PATHFINDER and EXPLORER population are presented). Avapritinib was associated with a significant improvement in OS, and in the DOT compared to midostaurin at first line, and cladribine and BAT at second line or later. Owing to limited reporting in the ECS, the relative effect on PFS could not be estimated. The EAG consider that there is substantial uncertainty in the IPTW, mainly due to concerns with the variables used for adjustment. In addition, the EAG were unable to evaluate the IPTW in its entirety, owing to a lack of detail on the methods of adjustment or results. The company also present a MAIC of the avapritinib studies and two midostaurin studies (D2201 and A2213). Only a small number of analyses presented in the MAIC report (provided in response to clarification questions) were relevant to the decision problem, as many analyses included populations who did not receive a starting dose of 200 mg of avapritinib. Avapritinib was associated with greater OS compared to midostaurin (all lines of therapy) but the confidence intervals crossed one; PFS was also improved for those receiving avapritinib compared to midostaurin. However, the MAIC is also subject to uncertainty, as the population is adjusted to the aggregate data from the midostaurin studies, and adjustments for key prognostic variables were not possible.

Finally, the reliability of the findings in the ITCs is difficult to ascertain, the IPTW and MAIC do not present any analyses for the population relevant to this decision problem, meaning plausible comparisons cannot be made between the IPTW and the MAIC for patients receiving a 200 mg dose of avapritinib.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

4.1.1 Summary of company's submission

The company's systematic literature review did not identify any economic evaluations of avapritinib for the treatment of adults with AdvSM (see Appendix G of the CS for a detailed description of the searches and results of the review). One study was identified comparing midostaurin with standard of care (SOC) in patients with AdvSM but the methods and results of this study are only presented in abstract form.[38] Table 26 of the CS provides a summary of the one included study, Cariou et al. (2018), which used a partitioned survival model with a lifetime horizon to compare life years and quality-adjusted life years (QALY) for midostaurin versus SOC when no head-to-head data were available. The company also summarises the key features of the cost-effectiveness model used in NICE TA728 to evaluate midostaurin for AdvSM (Table 28 of the CS).[23]

4.1.2 Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 2 for details. The EAG considers that all relevant publications are likely to have been identified. Table 28 of the CS provides a comparison of the key features of the company's economic analysis with the previous NICE appraisal for midostaurin (TA728[23]), with differences in key elements highlighted in Section 4.2.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de-novo* model to compare the cost-effectiveness of avapritinib with relevant comparators in two separate treatment lines: (i) avapritinib compared with midostaurin in adult patients with AdvSM who have not received prior systemic therapies, i.e., as a first line treatment (1L population setting); and (ii) avapritinib compared with cladribine, or best available therapy (BAT) as a proxy for cladribine, in adult patients with AdvSM who have received prior systemic therapies, i.e., as a second and subsequent line treatment (2L+ population setting).

A partitioned survival analysis (PartSA) is used to estimate the long-term health outcomes and costs associated with progression and the clinical pathway of AdvSM in the UK. In the PartSA, the time-dependent risk associated with disease progression and death is modelled by extrapolating clinical trial endpoints from PATHFINDER to directly determine the proportion of patients alive and in the progressed (or progression-free) health state over time for avapritinib, while survival outcomes for the comparators are based on comparative data from the ECS and real world evidence for time on treatment as a proxy for progression-free survival (see Section 4.2.6.2). When patients discontinue

treatment, a switch to another treatment is not directly modelled in the PartSA but the impact of treatment switching is implicit in the survival outcomes and the changes to health state membership. A five-year treatment benefit for avapritinib is applied in the company's base case analysis.

Avapritinib is modelled to affect QALYs by increasing the proportion of patients who are alive and progression-free over time, which is associated with improved HRQoL relative to the comparators. One key difference between the modelled outcomes for avapritinib compared to the comparators in the company's base case is that a proportion of the cohort in the avapritinib arm have discontinued treatment before disease progression, while for the comparators' PFS is assumed to be the same as time on treatment (TOT), i.e., the model assumes that patients in the comparator arm discontinue treatment due to disease progression only, which means that no part of the cohort is off treatment before progression. The utility values for progression-free are applied in the model for the total progression-free cohort; therefore, avapritinib is modelled to receive QALY gains compared to the comparators for patients who interrupt treatment before progression.

Avapritinib is modelled to affect costs by increasing the time on treatment compared to the comparators, with associated drug acquisition costs, and increasing the proportion of the cohort who remain progression-free for longer, while decreasing the proportion with progressive disease and requiring palliative care at end of life. The largest component of cost difference between avapritinib and its comparators is drug acquisition costs, with a much smaller relative proportion associated with health state (progression-free and progressed disease) resource use and, for the comparison with cladribine or BAT, drug administration costs, while only a very small difference in costs is associated with adverse event and end of life palliative care costs.

The company's *de-novo* model uses a very similar approach to that used in the NICE technology appraisal for midostaurin (TA728), with the same partitioned survival model with three health states for progression-free (PF), progressed disease (PD) and death, over a lifetime horizon, but with a cycle length of one month (30.44 days) used in the company's base case compared to 4 weeks in TA728. The model structure incorporates the preference of the NICE committee in TA728 to consolidate the PF health state into one health state with a single utility value, rather than two PF health states based on initial response to treatment with different utility values. The source of data used to inform treatment effectiveness, time on treatment, and utility values in the model is based on evidence from the relevant treatment-specific clinical studies or real-world evidence and clinician input (see Table 28 of CS for comparison of key features of the company's analysis with TA728).

The EAG considers that the company's model differs from the previous NICE technology appraisal TA728 in the following key elements:

- The separation of the population setting by line of treatment, where the comparators differ depending on prior use of systemic therapies. This difference is partly a consequence of the availability of midostaurin since TA728, but it may also be linked to the anticipated Medicines and Healthcare products Regulatory Agency (MHRA) licensed indication for avapritinib, where the company is seeking GB marketing authorisation for the treatment of [redacted], while the EU marketing authorisation in March 2022 is restricted to the treatment of adult patients after at least one systemic therapy.
- The comparators differ as a consequence of the availability of midostaurin.
- The duration of treatment benefit for avapritinib is 5 years in the company's base case analysis compared to a 3-year relative treatment benefit used in TA728 for midostaurin.
- Time on treatment for avapritinib is based on the median duration of treatment from 13 patients who received avapritinib in the open-label compassionate use program in the UK rather than the median duration of treatment in patients treated with avapritinib in the pivotal PATHFINDER study. In contrast, the duration of treatment for patients initiating midostaurin in TA728 was based on the time to treatment discontinuation in the midostaurin clinical trial D2201.[23]
- In the absence of data for PFS for comparators, PFS is assumed to be the same as time on treatment. In TA728, comparator PFS was also not available and it was estimated by applying the hazard ratio for overall survival to the PFS curve for midostaurin; this approach is considered in a scenario analysis by the company.
- Utility values are mapped from EORTC QLQ-C30 data in PATHFINDER to EQ-5D-3L using a published mapping algorithm, whereas utility values were mapped from SF-12 data from D2201 onto EQ-5D-3L in TA728.
- The company's model structure allows for the inclusion of allo-HSCT via a parallel health state Markov model in a scenario analysis, which was not considered in TA728.
- In TA728, midostaurin met NICE's criteria for a life-extending treatment at the end of life. The company's updated base case results following EAG points for clarification meets a 1.2 QALY severity weighting in the 2L+ population setting.

The appropriateness and implications of these differences between the previous NICE appraisal for midostaurin and the CS for the treatment of adults with AdvSM are discussed in the relevant sections below.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 14.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate but there is uncertainty about the exclusion of data from the EXPLORER study for the treatment effects of avapritinib, which are based on PATHFINDER only, and the separation of the population by treatment line. The choice of data used for PFS and time on treatment is not considered appropriate.
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 (HRQoL) in adults.	The CS is appropriate. EQ-5D data were not available from the clinical studies. Instead, utility values are mapped from EORTC QLQ-C30 data in PATHFINDER to EQ-5D-3L using a published algorithm by Young et al (2015).[39]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
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	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.

CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.

4.2.2 Model structure

4.2.2.1 Summary of company's submission

The base case model is a PartSA that is used to simulate the time in three mutually exclusive health states: progression-free (PF), progressive disease (PD) and death over time (see Figure 26 of CS). The cohort enters the model in the PF health state and the transitions to the PD and death health states are defined by the time-dependent PFS and OS curves.[40] The PFS and OS curves are extrapolated beyond available data from studies in order to model a lifetime horizon. The survival curves also reflect the effects of subsequent treatment use following discontinuation of initial treatment, and the potential effects of prior use of systemic therapies in the 2L+ population setting. The PF and PD health states are subdivided into 'on primary treatment' and 'off primary treatment' to reflect treatment switches from the primary (initial) treatment to treatments post-discontinuation in the PF health state and post-progression in the PD health state (see Table 27 of CS); however, the EAG notes that no costs of subsequent treatments are included in the company's base case analysis.

In a scenario analysis, the company considers an additional model structure that allows for the inclusion of allo-HSCT, which is considered as a potential curative treatment option for a very small proportion of patients with AdvSM who achieve complete remission following systemic treatment. The allo-HSCT model structure is via a parallel health state Markov model, where a proportion of the PF cohort in the base case model may enter the health states associated with allo-HSCT, consisting of pre-allo-HSCT, post-allo-HSCT and death (see Figure 27 of CS). The CS states that "according to clinical expert feedback the rate of increased allo-HSCT eligibility and the data regarding outcomes following treatment with avapritinib and subsequent HSCT are subject to uncertainty". Therefore, allo-HSCT was excluded from the company's base case and the parameter inputs relating to the allo-HSCT model are presented in Appendix N of the CS.

4.2.2.2 Points for critique

The company's base case model structure is consistent with the final model structure used in TA728 (midostaurin), which was considered by the Appraisal Committee to be suitable for decision making. In the original model structure for TA728, two PF health states were included for sustained response and lack of response in order to allow the utility values for PF to differ depending on response to treatment. However, the committee had concerns about the reliability of the data on response rates and duration of response from the midostaurin trials in order to partition the PF health state into two states, and expressed the need to ensure consistency in the PartSA by also partitioning OS by response status, which was not done in the model structure for TA728. The EAG considers that the same

concerns also hold with the response data from PATHFINDER (and EXPLORER) for avapritinib. In addition, response data are not available from the ECS for the comparators. Therefore, the EAG considers the company's approach of not partitioning survival outcomes by response to be appropriate, given the lack of data available.

The EAG considers that the appropriateness of the company's PartSA is largely dependent on how complete and mature the observed data informing survival outcomes are, especially OS, and the extrapolation of these outcomes over a lifetime horizon (see Section 4.2.6.2); uncertainty about the long-term OS extrapolations will lead to uncertainty in the estimates of cost-effectiveness of avapritinib relative to its comparators. The main limitation of the extrapolated OS in the company's base case analysis is that it is estimated independent of PFS and other intermediate endpoints such as treatment response rates. The company's model does not consider survival outcomes for separate clinical events such as those for individuals with PD and pre- or post-progression deaths, which is likely to be affected by subsequent treatment use after discontinuation from the primary treatment.

In the modelled scenario that allows for the inclusion of allo-HSCT, the eligibility for allo-HSCT is informed by response rates for avapritinib from EXPLORER and PATHFINDER by using the matching-adjusted indirect comparison with the midostaurin studies, which are not used in the company's base case analysis. In Appendix 6 the EAG highlights a number of major concerns with the company's model for the inclusion of allo-HSCT, largely related to the hypothetical nature of several key parameters and the oversimplification of the model. The EAG concludes that the allo-HSCT model is not suitable for decision making and is therefore not explored further by the EAG. The EAG also notes that in the CS it is highlighted that clinical expert feedback received by the company indicates that data regarding outcomes following treatment with avapritinib and subsequent allo-HSCT is uncertain. Therefore, the company excluded the allo-HSCT health state model from its base case.

4.2.3 Population

4.2.3.1 Summary of company's submission

The population considered in the model is adult patients with AdvSM, [redacted] However, in the model, the population is separated by line of treatment, where the comparators differ depending on prior use of systemic therapies, and the cost-effectiveness results for avapritinib are presented separately by line of treatment:

1. Avapritinib compared with midostaurin in adult patients with AdvSM who have not received prior systemic therapies, i.e., as a first line treatment – the 1L population setting; and
2. Avapritinib compared with cladribine, or best available therapy (BAT) as a proxy for cladribine, in adult patients with AdvSM who have received prior systemic therapies, i.e., as a second and subsequent line treatment – the 2L+ population setting.

The population is based on the baseline characteristics of patients from the safety population of PATHFINDER with a starting dose of 200 mg, and is separated by patients in the 1L and 2L+ settings, with a mean age of 68 years for 1L and 67 years for 2L+, proportion of male patients 53% for 1L and 61% for 2L+ setting, while the mean weight of 72 kg is the same across both population settings (see Table 31 of CS).

Subgroups by disease subtype (ASM, SM-AHN and MCL) are not considered in the economic analyses due to small patient numbers; in EXPLORER and PATHFINDER, patient numbers in the ASM and MCL subgroups treated with avapritinib in the 1L setting was less than 15, which was not considered by the company to be sufficient to perform statistically meaningful analysis. In addition, baseline characteristics for each subtype are not reported in the comparator evidence.

4.2.3.2 Points for critique

The EAG's primary concern in relation to the population used in the model is the separation of the population by line of treatment, which is not sufficiently justified in the CS and a separate cost-effectiveness analysis of avapritinib is presented for those who have received prior systemic therapies from those who have not. In TA728, the NICE recommendation for midostaurin is not restricted to the 1L population setting. Whilst it is clear that the majority of patients are likely to be treated at first line with midostaurin in the NHS, there are some patients (mainly historic) who will receive midostaurin as a second line treatment; this is reflected in the company's separate comparison with BAT (as a proxy for cladribine) in the 2L+ population setting, where BAT consists of a mixture of therapies, including [redacted]% of patients receiving midostaurin. The EAG believes that there is merit in assessing the cost-effectiveness of avapritinib compared with midostaurin in the overall population, i.e., not separated by line of treatment. This would involve using data from the entire ECS for midostaurin, who had received ≥1 line of systemic therapy (not necessarily as 1L) for AdvSM and data for avapritinib from PATHFINDER (and/or combined with EXPLORER 200 mg OD), with an adjustment made to balance for differences in treatment lines using the propensity weights; this also avoids discarding data by prior use of systemic therapies, which is necessary when splitting the data by treatment line. Importantly, whether the overall population is considered or split by prior use of systemic therapies, the evidence informing survival outcomes should make any necessary adjustments for potential confounding effects of both prior and subsequent treatment use.

The EAG is reasonably satisfied that the baseline characteristics of patients from PATHFINDER are generalisable to the UK NHS. Out of the 13 patients from 11 centres in the UK who received avapritinib as part of the open-label compassionate use program,[17] the median age was 68.8 years (range 57-76), which is similar to the mean age of 68 and 67 years used in the model for the 1L and 2L+ populations, respectively.

A major limitation of the company's economics analysis is that comparative analyses were not carried out for the disease subtypes of AdvSM, where survival times before the introduction of midostaurin are reported to vary from 2 months for people with MCL, 3 years for people with SM-AHN and 6 years for people with ASM [41] [2].

4.2.4 Intervention and comparators

4.2.4.1 Summary of company's submission

The intervention is avapritinib with a recommended starting dose of 200 mg taken once daily (OD) orally. This is aligned with the regimen used in PATHFINDER, with two patients who received a lower starting dose of 100 mg excluded from the analysis. Treatment with avapritinib is not recommended in patients with a platelet count of less than 50 x 10^9/L.

The draft SmPC states that patients should "[redacted]". Participants in the PATHFINDER trial discontinued treatment mainly due to disease progression or intolerability (see Section 3.2.1.2). Therefore, the model does not incorporate a stopping rule for avapritinib and patients are assumed to remain on treatment until discontinuation, which is defined by the time on treatment or progression curve, whichever comes first.

The comparators, which are defined as current clinical management in the UK, are dependent on the line of treatment and differ in the 1L and 2L+ population settings. Midostaurin is the only licensed therapy, and recommended by NICE in the overall population, for the treatment of AdvSM in the UK.[23] Therefore, the company have positioned midostaurin as the only relevant comparator in the 1L population. In the 2L+ population, the company have compared avapritinib with cladribine and a separate comparison with BAT as a proxy for cladribine, whereby clinical efficacy (including OS) stems from a mixture of therapies, including midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%).

The economic modelling consists of the following analyses:

- Patients who did not receive prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE populations of PATHFINDER (September 2022 data cut-off) compared to 1L patients receiving midostaurin in the ECS.

- Patients who received prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE populations of PATHFINDER (September 2022 data cut-off) compared to all patients who received cladribine as second line or later (2L+) therapy in the ECS.
- Patients who received prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety and RAC-RE populations of PATHFINDER (September 2022 data cut-off) compared to all patients who received BAT (basket of therapies) as second line or later (2L+) therapy in the ECS.

For the comparison of avapritinib with BAT, the drug acquisition cost associated with the BAT basket of therapies is set equal to the drug acquisition cost of cladribine. The CS states that this comparison is a proxy for the comparison of avapritinib with 2L+ cladribine.

Subsequent treatment use after discontinuation from primary treatment is not explicitly modelled. Allo-HSCT is considered as a potential treatment option for a very small proportion of the cohort who achieve remission with avapritinib in a separate scenario analysis (see Appendix 6).

4.2.4.2 Points for critique

Midostaurin is the only licensed therapy for the treatment of AdvSM in the UK and is recommended by NICE in the overall population, i.e., not restricted to 1L only. Whilst the EAG acknowledges that the majority of patients are likely to be treated 1L with midostaurin in current NHS clinical practice, there are some patients who will receive midostaurin at 2L+. At the clarification stage, the EAG requested clarification on why a separate comparison of avapritinib with midostaurin is not considered in the 2L+ population (question B1c). The company response states that discussions with UK clinical experts support the view that midostaurin is not commonly used in the 2L+ population. The clinical experts added that if patients discontinued 1L avapritinib treatment due to disease progression or adverse events leading to intolerance, then it is probable that these patients would also face difficulties tolerating midostaurin. The clinical experts supported the view that midostaurin would only be considered a viable option at 2L+ in a restricted number of patients, where treatment discontinuation is prompted by non-haematological toxicities, or as a last resort when lacking in any other treatment options, even though the chance of benefit is low.

Whilst the EAG is comfortable with the position that midostaurin is unlikely to be used as a subsequent therapy after 1L treatment, except in a minority of patients, the EAG notes that midostaurin is included in the comparison of avapritinib vs. 2L+ BAT, with [redacted]% receiving midostaurin in the historical ECS at 2L+. The EAG considers that the comparison of avapritinib with 2L+ BAT, excluding midostaurin, would be more appropriate in the 2L+ population in light of the view that midostaurin is not commonly used 2L+. In response to EAG clarifications (question B2d),

the company indicates that the comparison of avapritinib with 2L+ BAT (mixture of therapies) was only included to increase the size of the cohort of patients informing the comparison in the 2L+ population for cladribine. The company highlights that cladribine is the relevant treatment option in the 2L+ population, but in the comparative analysis from the ECS only a small number of patients were treated with 2L+ cladribine (n=23) and although improved OS was observed for patients treated with avapritinib compared to cladribine, it did not reach statistical significance. As a result, the company included a comparison of avapritinib with a larger cohort of 2L+ BAT (n=70), including all common therapies (midostaurin [redacted]%, cladribine [redacted]%, interferon alpha/peg-interferon alpha [redacted]%, and hydroxyurea [redacted]%), where a statistically significant improvement in OS was demonstrated when comparing 2L+ avapritinib to 2L+ BAT, which the company considers to be a reasonable proxy for cladribine following prior systemic therapy use.

The EAG considers that the separation of the population by treatment line is unhelpful in this context because it has resulted in treatment comparisons that are determined by increasing the sample size due to the immaturity of the available survival data (e.g., including a larger cohort of 2L+ BAT) rather than reflecting the likely treatment pathway for AdvSM in the UK. The EAG considers the relevant treatment comparison to be:

Avapritinib → cladribine vs. Midostaurin → cladribine

where avapritinib is considered as a potential treatment option to replace the best available standard of care in the NHS, which is midostaurin, while off-label cladribine is only considered as a subsequent treatment option where midostaurin (or avapritinib) fails or is not tolerated. However, in order to compare avapritinib with midostaurin in the overall population that is not separated by treatment line, the impact of prior midostaurin use on avapritinib survival outcomes needs to be appropriately accounted for. In the safety population of PATHFINDER for 2L+, a very high percentage of patients (83.6%) received midostaurin as prior systemic therapy, which means that less than 20% of the 2L+ cohort from PATHFINDER (corresponding to 11 patients) is available to consider outcomes in patients who did not receive prior midostaurin. Therefore, the limited number of patients in PATHFINDER safety population who were treatment naïve (n=38) and the immaturity of the survival outcomes appears to have resulted in the need to separate the population into those who are treatment naïve (1L) and those who had previously received a systemic therapy (2L+), with alternative comparators considered at each treatment line. The EAG would have liked to have seen an analysis comparing avapritinib with midostaurin in the full population for all treatment lines, with an adjustment made to balance for differences in treatment lines using propensity weights in the IPTW; additional data from EXPLORER 200 mg OD (n=20) may support this analysis by increasing the available sample size for avapritinib, as used in the company's MAIC analysis (see Section 3.4.3).

Subsequent treatment use after discontinuation from primary treatment is not explicitly modelled in the 1L or 2L+ populations. The EAG requested clarification (question B1b) on the numbers of patients who received subsequent therapies in PATHFINDER following discontinuation from avapritinib and the impact of subsequent treatment use on survival outcomes. The company were unable to provide this information due to insufficient data collected post-avapritinib discontinuation. Of a total of 10 patients across PATHFINDER and EXPLORER with partial records following discontinuation from avapritinib, [redacted] patients pursued transplant options ([redacted] out of 5 records for patients in PATHFINDER), while the remaining patients received "other treatment options". The company also states that UK clinical experts indicate that switching to subsequent therapies is not clinically relevant, with the majority of avapritinib treated patients either continuing with treatment or receiving allo-HSCT; the clinical experts supported the view that midostaurin would only be considered a treatment option post-avapritinib discontinuation in a restricted number of patients. The company states that they have taken a conservative approach to subsequent treatment use by assuming that all subsequent treatment costs are set to £0 in the model. Whilst the information on subsequent treatment use from PATHFINDER is limited, the EAG has a concern about the potential imbalance in the use of subsequent therapies following discontinuation from avapritinib versus discontinuation from midostaurin and the potential confounding of subsequent treatment effects on survival outcomes reported in PATHFINDER. The CS promotes the use of avapritinib as providing a bridge to the only potential curative treatment option for patients with AdvSM of allo-HSCT on the basis that a small proportion of patients treated with avapritinib can achieve complete remission and are, therefore, potentially eligible to pursue transplant options; however, the costs of allo-HSCT are not included in the company's base case analysis and it is unclear if the survival gains observed for avapritinib are confounded by the benefits of allo-HSCT or other subsequent treatment use.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a lifetime time horizon (until 99.99% of the cohort have died). A 3.5% annual discount rate is used for both costs and health effects.

4.2.5.2 Points for critique

The CS adheres to the NICE health technology evaluations manual[42] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The model includes four elements relating to treatment effectiveness and extrapolation of effects over time, by treatment initiated:

(i) Overall survival, i.e., the probability of all-cause death;
(ii) Progression-free survival, i.e., the probability of not progressing to the progressive disease health state;
(iii) Time on treatment, i.e., the expected duration on treatment until discontinuation due to disease progression, intolerability, or other reasons; and
(iv) Duration of treatment benefit for avapritinib, i.e., the length of time in the model that the treatment effects on progression and survival rates for avapritinib are maintained.

The data sources informing each of these elements for each treatment are described below and the corresponding time-dependent curves used in the company's base case analysis are presented in Figure 1, Figure 2, and Figure 3 for the comparisons with 1L midostaurin, 2L+ cladribine, and 2L+ BAT (proxy for cladribine), respectively.

The effectiveness of avapritinib in the model is based on time-to-event data from PATHFINDER (September 2022 data cut-off), which is used to estimate the OS and PFS extrapolation curves that are in turn used to determine health state membership (PF, PD or death) over time. In the base case analysis, the Kaplan-Meier (KM) data for OS is based on the safety population from PATHFINDER, adjusted using IPTW for comparison with the relevant comparators from the ECS. In contrast, the KM data for PFS is based on the RAC-RE population that is used to evaluate response to treatment in PATHFINDER, but from the unweighted analysis because PFS is not reported (or only partially reported using alternative response criteria) in the ECS. Parametric fitting of KM curves using independent fitted models was used to extrapolate OS and PFS outcomes over a lifetime horizon. The company states that the selection of parametric models for the base case analysis was based on visual inspection of fit, statistical goodness of fit, and clinical plausibility of the long-term extrapolations according to two UK haematologist consultants when presented with the top three best fitting curves. The probability of death in the model is also capped at the age- and sex-matched general population values in order to ensure that the predicted survival does not exceed that of the general population survival.

Time on treatment (TOT) for avapritinib is sourced from a cohort of 13 UK patients from the CUP (see Section 3.2.3) for the overall population (i.e., not separated by treatment line) with a median duration of treatment of 16.56 months,[17] which was extrapolated over time using an exponential distribution fitted to the median duration of treatment. The TOT curve for avapritinib based on

extrapolating the KM data for duration of treatment from PATHFINDER adjusted for IPTW (with data available from both the safety and RAC-RE populations) is considered in a separate scenario analysis.

The duration of treatment benefit for avapritinib is assumed to be 5 years in the model, where after 5 years the rates of progression and survival for avapritinib are set equal to the rates for the comparator treatments, i.e., the treatment hazard ratio relative to the comparators is set equal to one (HR=1.0) at 5 years. The company makes this assumption based on the duration of response to avapritinib in PATHFINDER, where the proportion of patients continuing to respond at 42 months is 70.5% (95% CI, 43.5 – 97.4%), which the company states suggests that most patients will continue to respond for at least 3.5 years.

The effectiveness of the comparator treatments is based on data from the IPTW analysis from PATHFINDER and the historical ECS, which allows the derivation of weighted time-to-event KM estimates for OS extrapolation for each comparison. Parametric fitting of KM data using independent fitted models was used to extrapolate OS outcomes over a lifetime horizon and the selection of parametric models was based on the same approach as used for avapritinib. In contrast to OS, PFS data was not analysed in the ECS because disease progression was either not recorded or recorded in a way that was not consistent with the evaluative mIWG-MRT-ECNM response criteria used in PATHFINDER. As a consequence, the company uses the comparator TOT curves based on the median duration of treatment from the ECS unweighted analysis as a proxy for PFS for the comparators in the base case analysis. This corresponds to a median TOT, equal to PFS, of [redacted] months for 1L midostaurin, [redacted] months for 2L+ cladribine and [redacted] months for 2L+ BAT, which was extrapolated over time using an exponential distribution fitted to the median duration of treatment. In a scenario analysis, comparator PFS is estimated by applying the OS hazard ratio resulting from the IPTW ITC to the avapritinib PFS curve.

Table 15 provides a summary of the source of treatment effectiveness evidence used in the company's base case analysis for each line of treatment and comparator, while Figure 1, Figure 2, and Figure 3 show the corresponding survival curves used in the company's base case analysis for the comparisons with 1L midostaurin, 2L+ cladribine and 2L+ BAT, respectively.

Table 15 Source of treatment effectiveness evidence used in the company's base case analysis for each line of treatment and comparator.

Parameter	Comparison	1L vs. midostaurin	2L+ vs. cladribine	2L+ vs. BAT
OS	Avapritinib	PATHFINDER safety population (adjusted for IPTW) 1L population vs. MIDO	PATHFINDER safety population (adjusted for IPTW) 2L+ population vs. CLAD	PATHFINDER safety population (adjusted for IPTW) 2L+ population vs. BAT
	Comparator	ECS IPTW analysis for 1L MIDO	ECS IPTW analysis for 2L+ CLAD	ECS IPTW analysis for 2L+ BAT

PFS	Avapritinib	PATHFINDER RAC-RE population (unweighted analysis) 1L population	PATHFINDER RAC-RE population (unweighted analysis) 2L+ population	PATHFINDER RAC-RE population (unweighted analysis) 2L+ population
	Comparator	Set equivalent to TOT comparator	Set equivalent to TOT comparator	Set equivalent to TOT comparator
TOT	Avapritinib	CUP, overall population	CUP, overall population	CUP, overall population
	Comparator	ECS unweighted analysis for 1L MIDO	ECS unweighted analysis for 2L+ CLAD	ECS unweighted analysis for 2L+ BAT

Abbreviations: OS, overall survival; PFS, progression-free survival; TOT, time on treatment; MIDO, midostaurin; CLAD, cladribine; BAT, best available therapy.

Figure 1 Survival curves used in the company's base case analysis for the comparison of avapritinib with 1L midostaurin

Figure 2 Survival curves used in the company's base case analysis for the comparison of avapritinib with 2L+ cladribine

Figure 3 Survival curves used in the company's base case analysis for the comparison of avapritinib with 2L+ BAT

4.2.6.2 Points for critique

The EAG have a number of major concerns in relation to the treatment effectiveness evidence used in the model and the assumptions, which are likely to favour the cost-effectiveness of avapritinib relative to the comparators and increase uncertainty in the two separate populations. These concerns relate to:

(i) Sources of evidence used to inform relative treatment effect and the lack of consistency in the sources of data used to inform different model parameters;
(ii) Immaturity of the OS data used in the extrapolations and the potential confounding effects of prior midostaurin use on OS in the 2L+ population;
(iii) Lack of PFS data for the comparators and lack of consistency in assumptions used for PFS between avapritinib and the comparators;
(iv) Source of evidence used to inform TOT in the model;
(v) Uncertainty about the duration of treatment benefit for avapritinib relative to the comparators; and
(vi) Impact of subsequent therapies on survival outcomes after discontinuation from the initial treatment, with the costs and utility values associated with the use of subsequent therapies excluded from the model.

Sources of evidence used to inform relative treatment effectiveness in the model

The first concern in relation to the relative treatment effectiveness estimates used in the model is the lack of direct comparative effectiveness evidence from randomised controlled trials from which to estimate time-to-event endpoints, in particular OS and PFS. The open-label, uncontrolled, single-arm study of PATHFINDER does not provide evidence of the relative effectiveness of avapritinib compared with current treatment options. Whilst it is acknowledged that the feasibility of conducting a phase 3 trial in AdvSM is a challenge due to the rare disease population and the limited treatment options available, it might be expected that with the increased availability of midostaurin an RCT

comparing avapritinib vs. midostaurin in a 1L population would be feasible. In the absence of an RCT, the assessment of cost-effectiveness of avapritinib with the comparators relies on indirect comparisons with historical control data, where there are a number of concerns relating to the validity of the approaches and data used by the company (see Sections 3.2 - 3.4).

The second concern relates to the limited justification for the choice of data and populations used to inform the company's base case analysis, which is based on the IPTW analysis using PATHFINDER (September 2022 data cut-off) and the historical ECS for OS. Several analyses for indirect treatment comparisons of avapritinib compared to midostaurin and cladribine, both in separate populations for each treatment individually and across all lines of treatment, were performed in the clinical effectiveness sections of the CS and summarised in Table 11 of this report. These analyses included pooled data from EXPLORER and PATHFINDER (April 2021 data cut-off for both studies) with the ECS, and MAIC analyses using pooled EXPLORER and PATHFINDER data (April 2021 data cut-off) with the midostaurin single-arm studies of D2201 and A2213 for all treatment lines (not split by population).

The company justified the exclusion of data from EXPLORER in the economic analysis on the basis that only 20 patients received avapritinib at the expected UK licensed dose in this study, and sufficient data were available from the pivotal PATHFINDER study at the September 2022 data cut-off. The EAG considers this to be a very weak argument given the immaturity of the OS data from PATHFINDER at the September 2022 data cut-off. The OS data from the safety population for patients treated with 200 mg avapritinib starting dose in PATHFINDER is based on a total of 38 patients in the 1L population and 67 patients in the 2L+ population. Median OS had not yet been reached in either population. Therefore, the EAG considers that the immaturity of the OS data (and also the immaturity of the PFS data from the RAC-RE population, where median PFS had also not been reached) is a strong argument for combining the 200 mg dose populations from the EXPLORER and PATHFINDER studies, which would increase the total population sample size by approximately 20%. At EAG clarifications, the EAG requested an additional cost-effectiveness analysis based on combined data from EXPLORER (patients who received 200 mg avapritinib OD) and PATHFINDER from the latest data cut-off (question B3). In response to this request, the company made the EAG aware that an updated data cut from PATHFINDER (September 2023 data cut-off) was available and also a final data cut from the EXPLORER study (April 2023 final data cut-off), but that the adjusted KM curves with comparative data from the ECS (IPTW sample) for OS and the comparators using the most recent PATHFINDER data cut-off (September 2023 data cut-off) and the pooled PATHFINDER (September 2023 data cut-off) and EXPLORER (April 2023 final data cut-off) data will not be provided until a later date (date unknown). Until the EAG can consider the maturity of the survival data in the latest data cut from PATHFINDER, the EAG's major concern relates to the immaturity of

the OS and PFS data informing the company's base case cost-effectiveness analysis based on the earlier PATHFINDER September 2022 data cut-off.

The third concern relates to the lack of consistency in the sources of data used to inform the different survival parameters in the model. In Table 15, the EAG shows that the company uses the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW for the comparisons with the relevant comparators in the 1L and 2L+ populations, but uses the RAC-RE population unweighted analysis for PFS for avapritinib. More importantly, however, the TOT curve for avapritinib, which determines the time until treatment discontinuation due to disease progression or other reasons, is not informed by PATHFINDER and is therefore not consistent with the PFS and OS outcomes used in the model. Furthermore, the approach used to determine the probability of moving to the progressive disease health state, via the PFS and OS curves (i.e., time in PD state is informed by the OS curve minus the PFS curve), differs for avapritinib and the comparators, where the TOT curve is used as a proxy for PFS for the comparators but not for avapritinib. This mismatch of different sources of evidence to inform three inter-related parameters in the model (PFS, TOT and OS) is a major concern because it creates inconsistencies in the data used. Moreover, the duration of treatment, which is determined by the TOT and PFS curves, is a major driver of cost-effectiveness for avapritinib relative to the comparators because the duration of therapy drives the treatment costs and the duration of improved health-related quality of life associated with PFS compared to PD.

Immaturity of the OS data used in the extrapolations and potential confounding effects on OS in the 2L+ population

The OS data used in the company's base case analysis from PATHFINDER at the September 2022 data cut-off is immature. Median OS in the overall population had not yet been reached, with the KM estimate for OS of 79% (95% CI, 70.8% – 87.3%) at 24 months based on 49 out of 105 patients in the full AdvSM population – See Figure 12 of the CS. When considering prior systemic therapy use in PATHFINDER, which is used to separate OS by treatment line, median OS had not yet been reached in either cohort; in the 1L population, the KM estimate for OS is 88.5% (95% CI, 77.9% - 99.1%) at 24 months based on 20 out of 38 patients, while in the 2L+ population, the KM estimate for OS is 73.6% (95% CI, 62.3% - 84.9%) at 24 months based on 29 out of 67 patients – See Figure 13 of the CS.

The immature OS data is extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which lead to very different long-term survival outcomes (see, for example, Figure 28 of the CS). However, the extent to which the different parametric extrapolations have an impact on the cost-effectiveness results is constrained by the inclusion of a finite duration of treatment benefit of 5 years for avapritinib, i.e., a lifetime treatment benefit for avapritinib is not considered in the company's base case analysis and therefore the extrapolation curves for avapritinib only impact

the survival of avapritinib up to 5 years because after this time point the rate of survival for avapritinib is set equal to the rate of survival of the relevant comparator. The implications of the different parametric extrapolations for immature survival data and the interplay with the duration of treatment benefit is explored further in Section 6.

Importantly, the EAG emphasises the need to have more mature OS data to inform the model fitting and extrapolations over time because without this data, the reliance on immature survival outcomes may result in highly inaccurate estimates of survival benefit for avapritinib compared to the comparators in both population settings. The EAG is particularly concerned about the accuracy of the substantial OS benefit for avapritinib compared to midostaurin in the 1L population, which only falls at 5 years because of the finite duration of treatment benefit assumption (see Figure 1 above), while the OS benefit for avapritinib compared to cladribine or BAT in the 2L+ population is substantially smaller (see Figure 2 above). When taken at face value, this difference in OS appears to go against the intuition of expecting to observe greater survival benefit for avapritinib compared to cladribine, relative to the survival benefit for avapritinib compared to midostaurin, because cladribine is a less effective treatment option for AdvSM compared to midostaurin. The EAG acknowledges that the difference in OS for the comparators is a consequence of the separation of populations by treatment line, but it is unclear whether the effects of prior midostaurin use in approximately 80% of patients in the 2L+ population in PATHFINDER has had an impact on survival outcomes for avapritinib in this population. Importantly, the EAG notes that the difference in OS for avapritinib compared to the comparators in the 1L and 2L+ populations is the main driver for the difference in the estimates of cost-effectiveness observed between these two populations in the company's base case results.

The EAG considers that the updated data cut-off from PATHFINDER (September 2023) may help reduce uncertainty in OS estimates and may relieve some of the EAG's concerns in relation to the maturity of the data. Furthermore, the EAG considers it helpful to examine the OS outcomes from EXPLORER (final data cut-off) for the 20 patients that received the starting dose of 200 mg in order to assess whether the findings from EXPLORER are consistent with those of PATHFINDER. In addition, as noted previously, the EAG would like to see an analysis comparing OS for avapritinib with midostaurin in the full population for all treatment lines, with an adjustment made to balance for differences in the use of prior systemic therapies using propensity weights in the IPTW, in order to further understand the implications on OS of separating the population by treatment line.

Limited availability of PFS data for use in the model

PFS was not available from the ECS to enable an IPTW comparison with PATHFINDER. Therefore, the company uses the comparator's TOT curve as a proxy for the comparator's PFS curve in their base case analysis. In the absence of alternative PFS data, the EAG considers this approximation to be reasonable and is supported by the view that patients would remain on treatment until discontinuation,

which is defined by the TOT curve or progression, whichever comes first. However, by assuming that the comparator's PFS curve is the same as the TOT curve, the model is making a strong assumption that patients in the comparator arm discontinue treatment due to disease progression only, which means that no part of the cohort is off treatment before disease progression for comparators. The EAG considers this assumption to be reasonable in the absence of suitable alternative PFS data but only if the approximation holds for both avapritinib and the comparators.

One key difference between the modelled outcomes for avapritinib compared to the comparators is that a proportion of the cohort in the avapritinib arm have discontinued treatment before disease progression due to the application of separate TOT and PFS curves for avapritinib in the model, while for the comparators, PFS is the same as TOT, i.e., the model assumes that patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression. This is important for both total costs and health-related quality of life outcomes. In the model, the utility values for the PF health state are applied for the total cohort progression-free, regardless of whether the patient has discontinued treatment or not based on the TOT curve. Therefore, avapritinib is modelled to receive QALY gains compared to the comparators for patients who interrupt treatment before progression. The same issue holds for the costs of treatment because the PF health state is subdivided into an 'on treatment' and 'off treatment' state, where a proportion of the avapritinib cohort is 'off treatment' in the PF health state and therefore has no corresponding costs of treatment (i.e., no avapritinib acquisition costs after treatment discontinuation and no costs associated with subsequent treatment use are included in the model) but receives the improved QALYs associated with PFS, while no proportion of the cohort in the comparator arm is 'off treatment' in the PF health state. This inconsistency in the approach used for avapritinib and the comparators is a key driver of the cost-effectiveness results, particularly for the comparison of avapritinib with 1L midostaurin because the area between the PFS and TOT curves for avapritinib in this comparison is substantial (see above in Figure 1 for the area between the blue [PFS] and green [TOT] lines) relative to the area between these curves for the comparisons of avapritinib with 2L+ cladribine (Figure 2) and BAT (Figure 3). The implications of a consistent approach to PFS for avapritinib and the comparators, where the TOT curve for avapritinib is used as a proxy for PFS in the same way as the comparator TOT curve is used as a proxy for the comparator PFS is explored further in Section 6.

A second key concern relating to the PFS data used in the model is the immaturity of the PFS data for avapritinib from the RAC-RE population of PATHFINDER. The model relies on the PFS data from the 1L and 2L+ RAC-RE analysis for avapritinib, which is unweighted (i.e., no IPTW comparison with data from the ECS), given that the evaluation of response to therapy using the mIWG-MRT-ECNM response criteria was only possible in this population. Median PFS in the overall population

had not yet been reached at the September 2022 data cut-off, with the KM estimate for PFS of 76.5% (95% CI, 66.9% – 86.0%) at 24 months based on 36 out of 81 patients in the full AdvSM population – See Figure 10 of the CS. When considering prior systemic therapy use in the RAC-RE population of PATHFINDER, which is used to separate PFS by treatment line in the model, median PFS had not yet been reached in the 2L+ population; in the 1L population, the KM estimate for PFS is 89.4% (95% CI, 78.1% - 100%) at 24 months based on 16 out of 30 patients, while in the 2L+ population, the KM estimate for PFS is 68.8% (95% CI, 55.5% - 82.0%) at 24 months based on 20 out of 51 patients – See Figure 11 of the CS. The immature PFS data for avapritinib is extrapolated beyond the limited follow-up of the RAC-RE population of PATHFINDER using different parametric distributions, which lead to very different estimates of long-term PFS (see, for example, Figures 32 and 33 of the CS). However, as noted above for OS, the extent to which the different parametric extrapolations for PFS have an impact on cost-effectiveness is restricted to the first 5 years, where the rate of PFS for avapritinib is set equal to the rate of PFS of the comparator arm at 5 years.

More importantly, the EAG is concerned that the PFS data from the RAC-RE population (unweighted analysis) of PATHFINDER is inconsistent with the OS data from the safety population (IPTW sample) of PATHFINDER used in the company's base case analysis. For example, in Figure 1 above for the comparison of avapritinib with 1L midostaurin, the PFS curve for avapritinib is equal to the OS curve for avapritinib in the first 5 years from treatment initiation (i.e., up to the maximum time point for the duration of treatment benefit for avapritinib). This occurs because the extrapolated PFS data from the RAC-RE population (unweighted analysis) is greater than the extrapolated OS data from the safety population (weighted analysis) in the first 5 years, but in the model the PFS curve is capped at the OS curve so that PFS does not exceed OS. This is illustrated in Figure 4, which shows that the KM data for PFS (RAC-RE population, unweighted analysis) lies above the OS KM data (safety population, IPTW analysis) for the comparison of avapritinib with 1L midostaurin, except in the tail of the curve (corresponding to PFS data from only 2 patients). This means that in the comparison of avapritinib with 1L midostaurin, no proportion of the cohort in the avapritinib arm enters the progressive disease health state in the first 5 years of the model, i.e., the treatment benefit from initiating treatment with avapritinib is maintained for a full 5 years without any disease progression. The EAG considers this assumption to be unreasonable in light of the TOT curve used in the model for avapritinib (green line in Figure 1 above), based on a median duration of treatment of 16.56 months, which reflects treatment discontinuation due to disease progression or other reasons. The implications of the unreasonable PFS data for avapritinib used in the model, which when taken together with the inconsistent approach used for avapritinib PFS compared with midostaurin PFS (based on using TOT as a proxy for comparator PFS), is highly favouring the cost-effectiveness of avapritinib relative to 1L midostaurin. The EAG concludes that the PFS data from the unweighted RAC-RE population of PATHFINDER is unfit for purpose and, therefore, the only reasonable

approximation for PFS is to use the TOT curve as a proxy for PFS in both the avapritinib and comparator arms in the model, in order to ensure consistency across the intervention and comparators and consistency with OS – the implications of this approach are explored further in Section 6.

The EAG notes that the company adopted an alternative approach for comparator PFS in a scenario analysis by applying the OS HR (resulting from the IPTW ITC) to the parameterised avapritinib PFS curve. This approach relies on the assumption that the HR for OS holds for PFS and that the proportional hazard assumption is met. Even without this assumption, the EAG considers this approach to be invalid for the reason given above that the parameterised avapritinib PFS curve based on the unweighted RAC-RE population is unreliable due to the immaturity of the data and the absence of comparator PFS data from the ECS to appropriately weight the data for avapritinib. Therefore, the EAG concludes that the parameterised avapritinib PFS curve used in the company's base case analysis is unsuitable for informing PFS in the model.

Figure 4 Kaplan-Meier curves for PFS from the unweighted RAC-RE population of PATHFINDER and OS from the weighted safety population of PATHFINDER for the comparison of avapritinib with 1L midostaurin

Source of evidence used to inform TOT in the model

TOT is a critical parameter in the model in two ways:

(i) it determines the duration of therapy with associated drug acquisition costs, where the largest component of cost difference between avapritinib and its comparators is the drug acquisition costs; and

(ii) it provides a proxy for PFS that enables a more comparable basis for avapritinib and its comparators rather than the unreliable parameterised avapritinib PFS curve, which in turn

drives the treatment costs and the duration of health-related quality of life benefits associated with PFS compared to PD.

Therefore, the source of evidence used to inform the TOT curve in the model is critical to the assessment of cost-effectiveness of avapritinib. The company chose to source the TOT data for avapritinib from a small cohort of 13 patients treated with avapritinib in the UK as part of the CUP, where the median duration of treatment was 16.56 months for the full population, not separated by treatment line due to small patient numbers.[17] To generate a parametric curve for TOT, the company applies a simple exponential distribution to the median duration of treatment (see Figure 31 of CS). The company justified the use of CUP for informing the duration of treatment for avapritinib on the basis that it represents real-world evidence (RWE) and ensures a "fair and contextually relevant basis" for comparison with the comparators used in the model, which are also based on RWE from the ECS. The EAG considers this choice of TOT curve for avapritinib as a major limitation of the company's base case analysis on the grounds that: (i) it is not consistent with the OS outcomes used in the model; (ii) it is based on a very small cohort of 13 patients and only 9 of these patients received the starting dose of avapritinib 200 mg OD; (iii) the data is not separated by treatment line as required by the model because 10 out of the 13 patients received avapritinib as a first line regime; (iv) KM data for duration of therapy in CUP is not available (note that the full study report is not available, only an abstract reporting results) and therefore the company applied a simple exponential distribution to the median duration of treatment to derive a parametric curve over time; and, most importantly, (v) an IPTW ITC of avapritinib and the comparators is not used for the TOT curves in the model.

The EAG considers that the most appropriate TOT curve for avapritinib is based on extrapolating the KM data for duration of treatment from PATHFINDER safety population (to match that used for OS) adjusted for IPTW, which was considered by the company in a separate scenario analysis. Moreover, the IPTW sample from the ECS for TOT should be used for the comparators in the model rather than the unweighted median duration of therapy (with simple exponential distribution applied to the median duration) from the ECS that is used in the company's base case analysis. This ensures comparability between the duration of therapy for avapritinib and the comparators and consistency with the primary data source used to inform OS in the model, which is particularly important because the TOT curves are used as a proxy for PFS in the absence of alternative PFS data from the ECS.

The implications of using the parameterised IPTW outcomes from PATHFINDER and the ECS for TOT for avapritinib and the comparators rather than the median duration of therapy from CUP and the unweighted ECS for avapritinib and the comparators, respectively, are shown in Table 16. The parameterised IPTW outcomes from PATHFINDER and ECS [redacted] the median time on treatment for avapritinib (both treatment lines) and 1L midostaurin, but [redacted] the median time on treatment for 2L+ cladribine and 2L+ BAT. The resulting impact is [redacted] in

the TOT for avapritinib vs. 1L midostaurin and [redacted] for the comparisons with 2L+ cladribine and BAT. The implications for the cost-effectiveness results are explored in Section 6.

Table 16 Median duration of treatment in months from the parametric TOT curves used in the company's base case analysis and the EAG's preferred base case analysis

TOT curve	Comparison	1L vs. midostaurin	2L+ vs. cladribine	2L+ vs. BAT
Company base case: CUP for avapritinib and unweighted ECS for comparator	Avapritinib	16.4	16.4	16.4
	Comparator	[redacted]	[redacted]	[redacted]
	Difference:	[redacted]	[redacted]	[redacted]
EAG preferred base case: IPTW from PATHFINDER and ECS for avapritinib and comparators*	Avapritinib	[redacted]	[redacted]	[redacted]
	Comparator	[redacted]	[redacted]	[redacted]
	Difference:	[redacted]	[redacted]	[redacted]

*The values vary depending on the parametric distribution choice used to extrapolate the time on treatment curve. The EAG base case uses the curve selected by the company in their scenario analysis based on lowest AIC/BIC criterion.

Duration of treatment benefit for avapritinib

The duration of treatment benefit for avapritinib is assumed to be 5 years in the model, where after 5 years the time-dependent rate of progression and survival for avapritinib is set equal to the rate of the comparator treatment. This approach used by the company is analogous to that used in TA728 for midostaurin, except that a 3-year relative treatment benefit was used for midostaurin compared to BAT instead of 5 years. In TA728, the company's original base case analysis included a lifetime treatment benefit but the committee considered it implausible to retain the benefits of midostaurin over the long-term when patients no longer continue to receive treatment. The clinical experts advised that more sustained disease response is achieved while patients continue to receive midostaurin, but noted that disease response can be lost because of associated haematological malignancy instead of mastocytosis itself, while the effects of treatment dissipate rapidly after discontinuing treatment. The committee concluded that a 3-year midostaurin treatment benefit is likely to be optimistic for patients who stop treatment before 3 years, but is potentially pessimistic for the minority of patients who remain on treatment beyond 3 years, to an unknown extent.

The company justified the 5-year treatment benefit for avapritinib based on the rate of duration of response in PATHFINDER of 70.5% (95% CI, 43.5 – 97.4%) at 42 months in the RAC-RE population for all AdvSM (n=81). The EAG notes that the TOT derived from the parameterised IPTW outcomes from PATHFINDER and the ECS (Table 16 above) show that the median TOT for avapritinib is [redacted] months for the comparison with 1L midostaurin, but [redacted] in the 2L+ population setting ([redacted] months for the comparison with 2L+ cladribine and [redacted] months for the comparison with 2L+ BAT). Under the assumption that more sustained disease response is achieved while patients

continue to receive avapritinib, the TOT curve suggests that most patients will continue to respond to treatment for at least 3.5 years in the 1L population setting. The EAG's clinical advisors also supported the view that a longer duration of treatment benefit would be expected for avapritinib compared to midostaurin. Therefore, the EAG considers the assumption of a 5-year treatment benefit for avapritinib to be reasonable in the 1L population setting but acknowledges that this could potentially be pessimistic when using the TOT curves from the parameterised IPTW outcomes from PATHFINDER and the ECS for avapritinib, where approximately [redacted] of patients remain on treatment at 5 years and progression-free because TOT is used as a proxy for PFS in the comparison with midostaurin. Importantly, however, the EAG notes that there is an interplay between the survival parameters in the model of OS and PFS (informed by TOT) and the duration of treatment benefit assumed for avapritinib. Therefore, it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes assumed in the model; for example, if the extrapolation of OS based on immature data is highly optimistic, then an appropriate cap on the duration of treatment benefit is required. This interplay between survival outcomes and the duration of treatment benefit is explored further in Section 6 for each treatment line.

In summary, the EAG considers there to be important uncertainty about the duration of treatment benefit for avapritinib and the interplay with survival outcomes, and the most appropriate duration of benefit may differ depending on the population.

Impact of subsequent therapy use on survival outcomes

The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment is not considered in the company's base case analysis in the 1L or 2L+ populations. The company were able to provide only very limited information on treatments used post-avapritinib discontinuation from PATHFINDER, where [redacted] out of 5 records pursued transplant options. The EAG is concerned that there may be potential confounding of subsequent treatment effects on survival outcomes reported in PATHFINDER for avapritinib, but the costs and utility values associated with the use of subsequent therapies are excluded from the model. This is expected to only represent a concern for the proportion of the cohort who received allo-HSCT because other treatments options used post-progression would be expected to be the same for avapritinib and its comparators, and the cap of 5 years on the duration of treatment benefit for avapritinib means that there is no long-term differential in post-progression survival between avapritinib and the comparators in the model.

4.2.7 Adverse events

4.2.7.1 Summary of company's submission

The model includes 34 treatment-specific grade 3 and above AEs, which were identified based on a minimum incidence of 2% in patients treated with a dose of 200 mg OD of avapritinib from

PATHFINDER (September 2022 data cut-off, safety population). The incidence of AEs for midostaurin is based on data reported in the SmPC for midostaurin,[43] while the incidence of AEs for cladribine is based on data reported in Barete et al. (2015), which reports on the long-term efficacy and safety of cladribine in adult patients with mastocytosis based on the national reference centre in France that followed up 68 adult patients over the last decade[44] and SmPC for cladribine[45].

The AEs included in the model have associated cost and decrements in HRQoL, which are reported in Section 4.2.9.5and Section 4.2.8, respectively. In the company's original submission, all AEs were assumed to last 14 days but no justification was provided for the duration of events. In response to EAG clarifications (question B9b), the company revised the model by applying event-specific durations for each AE and assuming a duration of 22.84 days for the events' whose duration are not reported elsewhere (see Table 43 of CS for the source of AE disutilities and duration of events used in the model) based on the average of the known event-specific durations. In response to EAG clarifications, the company also provided an updated set of per cycle probabilities of AEs for avapritinib based on pooled data from PATHFINDER (September 2023 data cut-off) and EXPLORER (final April 2023 data cut-off). The per cycle probabilities and durations of AEs used in the company's updated base case analysis following EAG clarifications are summarised in Table 17.

Table 17 Per cycle probabilities and durations of adverse events used in the company's updated base case analysis

Adverse event	Intervention per cycle probability			Duration (days)
	AVA	MIDO	Cladribine	
Thrombocytopenia	0.00527	0.00000	0.01434	23.230
Anaemia	0.00687	0.00000	0.01642	16.070
Other haematological disorders	0.00141	0.00245	0.01061	24.846
Gastrointestinal bleed	0.00018	0.00036	0.00000	22.844
Acute myeloid leukaemia	0.00017	0.00021	0.00000	22.844
Sepsis	0.00035	0.00080	0.00098	34.000
Hearth failure or shock	0.00000	0.00007	0.00000	22.844
Cardiac arrest	0.00035	0.00000	0.00000	22.844
Cerebrovascular accident, nervous system infections, or encephalopathy	0.00000	0.00000	0.00000	22.844
Haemorrhagic cerebrovascular disorders	0.00000	0.00000	0.00000	22.844
Non malignant gastro-intestinal tract disorders	0.00038	0.00047	0.00000	25.110
Non malignant hepatobiliary or pancreatic disorder	0.00028	0.00070	0.00000	22.844
Pneumonia	0.00017	0.00072	0.00000	14.000
Pleural effusion	0.00035	0.00043	0.00000	22.844
Low back pain	0.00018	0.00000	0.00000	22.844
Hypertension	0.00053	0.00000	0.00000	22.844
Syncope or collapse	0.00053	0.00000	0.00000	22.844
Unspecified oedema	0.00071	0.00021	0.00000	22.844
Tendency to fall, senility or other condition affective cognitive functions	0.00000	0.00000	0.00000	22.844
Fever of unknown origin	0.00000	0.00043	0.00055	12.300
Breast disorders	0.00000	0.00000	0.00000	22.844
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	0.00041	0.00048	0.00000	33.415
Sleep disorders	0.00000	0.00000	0.00000	22.844
Other respiratory disorders	0.00029	0.00026	0.00000	12.720
Headache, migraine or cerebrospinal fluid leak	0.00000	0.00011	0.00000	22.844
Peripheral vascular disorders	0.00017	0.00014	0.00000	8.000
Kidney or urinary tract infections	0.00000	0.00000	0.00000	22.844
Skin disorders	0.00035	0.00014	0.00000	34.000
Weight increased	0.00071	0.00000	0.00000	22.844
Appendicitis	0.00053	0.00000	0.00000	22.844
Chronic Kidney disease	0.00053	0.00000	0.00000	22.844
Cognitive disorder	0.00053	0.00000	0.00000	22.844
Renal failure	0.00053	0.00000	0.00000	22.844
Non-malignant, ear, nose, mouth, throat or neck disorders	0.00000	0.00028	0.00000	22.844

4.2.7.2 Points for critique

The EAG has no major concerns with the approach used by the company to model AEs. The EAG conducted a scenario on the company's base case analysis by turning off all AEs to assess the impact of AEs on total costs and QALYs. The results of this scenario confirm that the AEs have a very minor impact on total costs and QALYs and there are no major differences in AEs between avapritinib and the comparators. Therefore, AEs are not considered further by the EAG.

4.2.8 Health-related quality of life

4.2.8.1 Summary of company's submission

The CS considers HRQoL relating to: (i) health state utility values, stratified by treatment line; (ii) disutilities associated with AEs; and (ii) disutility associated with mode of treatment administration. Health state utility values are applied to time spent in health states in the model in order to calculate quality-adjusted life years (QALYs) that reflect the improvement in health-related quality of life (HRQoL) associated with treatment. The company conducted a systematic literature review to identify studies reporting HRQoL for patients with AdvSM (see Appendix H of CS for details about the systematic literature review, including methodology, inclusion criteria and results), but no relevant studies were identified. The EAG appraisal of health-related quality of life evidence identification is presented in Appendix 3.

EQ-5D data were not available from either PATHFINDER or EXPLORER. EORTC QLQ-C30 from the RAC-RE population of PATHFINDER (September 2022 data cut-off) were mapped onto the EQ-5D-3L using a published algorithm by Young et al., (2015) [39] derived from UK tariffs which was identified through a targeted literature review (TLR) conducted to identify the availability of mapping algorithms from EORTC QLQ-C30 to EQ-5D-3L (see Appendix P1 of CS). The mapped utility values for each individual across all observations prior to progression were averaged to derive a single utility value for the PF health state, which was estimated to be [redacted] (standard error [SE]: [redacted]) for the 1L population and [redacted] (SE: [redacted]) for the 2L+ population.

There was only one observation for PD, even when pooling observations from PATHFINDER and EXPLORER. Therefore, the company conducted a TLR to identify a relevant health state utility value for post-progression in AdvSM (see Appendix P2 of CS). The search strings extended to include the haematological neoplasms typically associated with AdvSM. The EAG appraisal of targeted literature reviews is presented in Appendix 5. Of the six identified studies[46-49] [50] [51] (see Table 8 Appendix P2 of CS), four[46-49] were used to calculate a ratio between the PD and PF utility values reported in each study. All four studies included patients with acute myeloid leukaemia (AML) – see Table 42 of CS. To create an aggregate ratio across the four studies, a weighted average of the ratios in each study was derived (with the number of patients included in each study used to define the weights) of [redacted] and

this ratio applied to the PF utility values for the 1L and 2L+ populations to estimate a utility value for the PD health state, in each population separately. The PD utility values used in the model are [redacted] for the 1L population and [redacted] for the 2L+ population (with a standard error of 10% of the mean value assumed in the probabilistic analysis). Table 44 of the CS summarises the health state utility values used in the company's base case analysis.

The health state utility values were adjusted for ageing in the model in response to EAG clarifications (question B8). The utility values are not permitted to exceed the gender and age-adjusted UK general population norms. Disutilities associated with grade 3+ AEs are included in the model (Table 43 of CS). A one-off decrement in utility associated with mode of treatment administration of 0.074 is applied for cladribine, in line with the approach used in NICE TA728.[23]

4.2.8.2 Points for critique

The total QALYs estimated for the treatments is primarily determined by the time spent in the PF and PD health states and the corresponding health state utility value. The disutilities associated with AEs and the mode of administration for cladribine have minimal impact on the cost-effectiveness results.

PF health state utility

In the absence of EQ-5D data from PATHFINDER or EXPLORER, the EAG considers the approach used by the company to map from the EORTC QLQ-C30 instrument to EQ-5D to derive the PF health state utility value to be appropriate. The EAG considers the mapping algorithm from Young et al (2015)[39] to be the most suitable from amongst the available algorithms (see Table 3, Appendix P1 of CS) for the UK. However, the EAG is concerned about the limited data available from PATHFINDER to inform the PF utility value. The utility data is based on the PATHFINDER September 2022 data cut-off (i.e., not the latest September 2023 data cut-off) where there are a limited number of observations at each time point used to inform the mapped utility value associated with PF in the 1L and 2L+ populations, with missing data from the EORTC QLQ-C30 domains excluded from the analysis and no consideration given to data imputation methods. Table 18 shows the number of patients with EORTC QLQ-C30 data at each time point used to inform the mapped PF utility value in each population (see response to EAG clarifications question B7).

Table 18 Number of patients with EORTC QLQ-C30 data from PATHFINDER (September 2022 data cut-off) at each time point used to inform the mapped utility value associated with the PF health state for each population in the company's base case analysis

Study time point	Number of patients	
	1L population	2L+ population
Baseline	29	46
Week 2	23	42
Week 4	21	37
Week 8	21	30

Study time point	Number of patients	
	1L population	2L+ population
Week 16	16	25
Week 24	12	25
Week 32	16	19
Week 40	17	20
Week 48	-	-
Week 56	-	1
Week 64	10	12

The EAG requested clarification from the company (question B6b) on why HRQoL observations from EXPLORER (200 mg dose) were not combined with observations from PATHFINDER in order to increase the sample size. The company states that the observations were not combined in order to maintain consistency across the key efficacy parameters (OS, PFS and TOT) used in the model. The EAG considers that HRQoL data from EXPLORER could potentially augment the existing sample size by an additional 16 patients with EORTC QLQ-30 Global Health Score, which would supplement the small cohorts of 29 patients for the 1L population and 46 patients for the 2L+ population from PATHFINDER. The company have stated in response to EAG clarifications question B6a that an analysis with 2023 EXPLORER HRQoL will be provided at a later (undefined) date.

The EAG notes that no consideration in the CS was given to the derivation of time-dependent utility values from the available HRQoL observations up to week 64, where the mapped PF utility could be derived as a function of time and extrapolated over the long-term to allow for any potential changes in quality of life as a function of time since start of treatment.

In the model, the utility value for PF is applied for the total cohort progression-free over time. As noted previously, the company's base case analysis allows a proportion of the cohort in the avapritinib arm to discontinue treatment before disease progression, while for the comparator arm no part of the cohort discontinues treatment before progression. This means that avapritinib is modelled to receive improved HRQoL compared to the comparators for patients who interrupt treatment before progression because this proportion of the cohort is assigned the PF utility value. Therefore, the total QALYs gained for avapritinib relative to the comparators is sensitive to the PF utility value used in the model. Due to the limitations of the data, the EAG considers the utility value for PF to be uncertain. The EAG explores the impact of varying the PF utility value on the cost-effectiveness results in Section 6.

PD health state utility

The EAG considers the utility value associated with the PD health state to be highly uncertain. No studies have been identified that report a utility value for PD in AdvSM and only one observation for

PD was available from the pivotal studies, even after pooling observations from PATHFINDER and EXPLORER. The EAG has a number of concerns about the PD/PF utility ratio used in the company's analysis to derive a utility value for PD, including:

- Whilst all the included studies examined patients with AML, the generalisability of the utility values for patients with this disease condition to those with AdvSM has not been clinically validated;
- There is large variability in the PD/PF utility ratios across the four included studies: 0.41 in Stein 2018[46], 0.57 in Joshi 2019[47], 0.94 in Leunis 2014[48], and 0.99 in Mamolo 2019[49]. The causes and impact of these differences have not been explored or discussed in the CS;
- The mean age in all four studies, i.e., 44.3 (SE: 16.6) in Stein 2018[46], 44 (SE: 14.9) in Joshi 2019[47], 52.7 (SE: 12.8) in Leunis 2014[48] , 60 (SE: 15) in Mamolo 2019[49], is lower than the modelled population with starting age of 68.29 (SE: 6.83). The implications of this difference in age has not been explored or discussed in the CS;
- It is uncertain whether the estimated PD/PF utility ratio is equally applicable to the 1L and 2L+ populations as assumed in the company's base case analysis;

Therefore, the utility value for the PD health state is highly uncertain. However, it is unlikely to be a key driver of the cost-effectiveness of avapritinib relative to its comparators because there is no long-term differential in post-progression survival between the treatments in the model due to the cap of 5 years on the duration of treatment benefit for avapritinib. Also, subsequent treatment use post-progression has not been explicitly modelled in the company's analysis.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The company's base case analysis includes resource use and costs relating to: (i) drug acquisition; (ii) drug administration; (iii) health state (PF and PD) resource consumption; (iv) adverse events; and (v) end of life palliative care.

Costs are inflated to 2022/23 prices using the hospital and community health services (HCHS) pay and process index from the Unit Costs of Health and Social Care as obtained from the Personal Social Service Research Unit (PSSRU) report.[52] Costs are discounted at an annual rate of 3.5%. Table 19 summarises the costs included in the company's base case analysis.

Table 19 Costs used in the company's base case analysis

Item	Model	Source
Drug acquisition costs		
Avapritinib	[redacted] per cycle (monthly)	The recommended dose of avapritinib is 200 mg orally once daily. Avapritinib is available in 25 mg, 50 mg, 100 mg and

Item	Model	Source
		200 mg film-coated tablets, which each have a list price of £26,667.00 per pack of 30 tablets. A simple PAS fixed price of [redacted], which equates to a [redacted] discount off the list price has been confirmed. The per cycle cost includes 5% wastage in the base case.
Midostaurin	£24,398 per cycle (monthly)	The recommended dose is 100mg per day, which has a list price of £5,610 per pack of 56 tablets. Price taken from the British National Formulary (BNF).
Cladribine	£6,072 one-off cost	A one-off cost was applied to the first cycle of the model for patients initiating cladribine, prices estimated using BNF prices and the median cumulative dosage (2.25 mg/kg) and the median number of cycles (3.68) reported in Barete et al (2015).[44] This corresponds to five vials per treatment course with wastage included.
Ondansetron	£3.80 per cycle (monthly)	A daily 8mg anti-sickness tablet, with a list price of £1.25 per pack of 10 tablets, which is assumed to be prescribed to [redacted] of patients receiving midostaurin.
Cyclizine	£1.10 per cycle (monthly)	A daily 50mg antiemetic tablet, with a list price of £3.50 per pack of 100 tablets, which is assumed to be prescribed to [redacted] of patients receiving midostaurin.
Drug administration costs		
Avapritinib	None	Drug administered orally so no administration costs included.
Midostaurin	None	Drug administered orally so no administration costs included.
Cladribine	£8,527 one-off cost	Cost uses NHS reference costs 2021/22 and was based on a previous HTA submission in AdvSM (NICE TA728). Three costs incurred: delivering complex chemotherapy at first treatment (£435), delivering subsequent chemotherapy (£384), and hospitalisation days (£543). In line with assumptions made in NICE TA728 and clinical opinion, 65% of patients were assumed to received cladribine in an outpatient setting during the first cycle, while 35% were assumed to be hospitalised for 9 days. In the remaining cycles only 5% of the administrations were assumed to occur in an inpatient setting.
Health state resource use (progression-free and progressed disease)		
Progression-free state	0 - 6 months: £1,304.50 per cycle 6 - 12 months: £774.30 per cycle 12 months +: £406.70 per cycle	The PFS was split into 6-monthly cycles (0-6 months, 6-12 months and 12 months onwards) to capture the frequent resource use associated with monitoring patients. The approach used is in line with NICE TA728 (midostaurin). Table 49, page 165 of the CS provides details of all resource categories. Unit costs were derived from NHS reference costs 2021/22 and latest PSSRU published costs.
Progressed disease state	£226.20 per cycle	Estimated using the same method as the progression free state.
Adverse events (AEs)		
Adverse event costs	Costs range from £702 for unspecified oedema to £4,753 for Acute myeloid leukaemia (Table 51, page 166, of CS)	The unit costs associated with the management of AEs considered in the economic model are taken from the NHS reference costs 2021/22 and in the case of the drug administration procedures, the aggregate cost of each AE was calculated by averaging the associated NHS codes.
End of life palliative care costs		
Palliative care	£6,836 one off cost	This transition to the death state in the model is associated with palliative care costs, which are based on Round et al. 2015 for different types of cancer (an average of breast, colorectal, lung and prostate cancer) and inflated to 2022/23 price.

4.2.9.2 Drug acquisition and administration costs

Avapritinib is available in 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets, which each have a list price of £26,667 per pack of 30 tablets and a simple PAS fixed price of [redacted]. The recommended dose of avapritinib is 200 mg orally once daily. The company assumes 15% of patients reduce their dose to less than 100mg dosage (either 25 or 50 mg). The company states discussions with two consultant haematologists in the UK suggests minimal wastage resulting from switching of doses and the model includes 5% wastage in the company's updated base case analysis. There are no administration costs for avapritinib or midostaurin, which also corresponds to TA728.

Midostaurin is available in 25 mg capsules. The recommended dose is 100 mg per day, which corresponds to four units per day. The CS states that, according to clinical experts, [redacted] of patients decrease midostaurin dosage to 50 mg twice daily, with [redacted] of patients returning back to the full dosing. Therefore, it was assumed that an average of [redacted] of patients would receive the reduced dosage across all timepoints. In the model the company applies a weighted average ((100mg * [redacted] of patients) + (50mg * [redacted] of patients) = [redacted] dose per day). The CS states that there is a scarcity of data on drug wastage for midostaurin; therefore, the company does not include wastage in its base case analysis.

Cladribine is given at a dosage of 0.14 mg/kg, 5 times per month. The cost of cladribine administration in the CS (£8,527) is very similar to that used in TA728 (£8,634) as the same broad methodology was used, with only some minor variations to the cost categories included; both submissions include the costs of initial and subsequent chemotherapy, but the CS includes hospitalisation costs, whereas in TA728 costs of other haematological and splenic disorders and nurse costs were included.

The CS includes a once daily anti-sickness tablet, 8mg ondansetron, for [redacted] of those receiving midostaurin, with a list price of £3.47 per pack of 100 tablets. An alternative daily anti-sickness tablet of cyclizine for 5% of patients, with a list price of £1.25 per pack of 10 tablets is also included. In TA728, nausea and vomiting were included as AEs, with an associated unit cost of £182 (obtained from previous NICE technology appraisals [TA400 and TA460]) but the prevalence of this AE when taking midostaurin is redacted in TA728.

Points for critique

The EAG appraisal of cost and healthcare resource evidence identification is presented in Appendix 4. The EAG has no major concerns relating to the drug acquisition and administration costs used in the model. However, the EAG considers that the relative dose intensity and the implications for drug wastage is uncertain for both avapritinib and midostaurin. In response to EAG clarifications (question B12a), the company states that UK clinical experts indicate that most patients are prescribed a 28-day

supply of avapritinib initially and are expected to remain on the prescribed dose for at least 2-3 weeks before modifying the dose, with the majority of dose reductions to 100 mg, and that patients are closely monitored every 2-4 weeks in the first 3 months of starting treatment. The company updated the model in response to EAG clarifications to include a relative dose intensity of 15% for patients receiving avapritinib (initially 0% in the CS), with corresponding drug wastage of 5%. For midostaurin, the CS states that there is limited data available on drug wastage; therefore, the company does not include wastage for midostaurin in its base case analysis.

The EAG's clinical advisors did not consider the anti-sickness tablet of 8 mg ondansetron OD to be the most commonly prescribed anti-sickness medication in the NHS for patients receiving midostaurin because cheaper alternatives are available. In response to EAG clarifications (question B11), the company states that following consultation with UK clinical experts, the experts agreed that ondansetron is prescribed as the default medication but some patients may occasionally require more antiemetics or antidiarrheals. To reflect this, the company updated the base case analysis to include 5% of patients receive cyclizine 50 mg three times a day. The EAG assessed the impact of the anti-sickness medication costs on the cost-effectiveness results by removing them from the model for midostaurin; this resulted in a negligible impact on the total costs of midostaurin.

4.2.9.3 Confidential pricing arrangements for drug acquisition costs

The EAG notes that there is a confidential commercial arrangement in place for the comparator of midostaurin. The drug acquisition cost used in the CS and in Sections 5 and 6 of this report include only the confidential pricing agreement for avapritinib. The EAG also notes a change to the eMIT prices for ondansetron and cyclizine.

Table 20 presents details of the comparator with a confidential price which differs from the publicly available list price used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of 19th March 2024.

Table 20 Source of the confidential prices used in the confidential appendix

Treatment	Form	Dose per unit	Pack size	Source of price used in model/type of confidential arrangement sent by NICE
Midostaurin	Oral tablet	25 mg	56	cPAS
Ondansetron	Oral tablet	8mg	10	eMIT
Cyclizine	Oral tablet	50mg	100	eMIT

Abbreviations: cPAS, confidential patient access scheme.

4.2.9.4 Health state resource use

Resource use for patients in the PF or PD health states are included and are the same regardless of treatment received. Additionally, in the PF health state resource use is stratified by time in state from zero to six months, six to twelve months, and twelve months and over, primarily to capture the more frequent resource use associated with monitoring patients in the initial treatment phase. The resource use was estimated via a questionnaire answered by two consultant haematologists, with the categories listed in Table 49, page 165 of the CS. The total cost of disease management per health state was estimated by multiplying the resource use by the unit costs derived from NHS reference costs 2021/22 and latest PSSRU published costs.

Points for critique

The EAG considers the health state resource use used in the model to be broadly appropriate. In TA728 the same resource use (with the addition of GP home visits), in relation to the same health states and time periods, were based on responses from 5 clinical experts. The resource use estimates and resulting health state costs per model cycle are redacted in TA728. The unit costs are broadly the same as those used in the CS.

4.2.9.5 Adverse event costs

There are 34 AE costs included in the company's model (although two of them have zero costs: weight gain and renal failure). Haemorrhagic cerebrovascular disorders (£3522.20) is included in the model, but not listed in Table 51, page 166, of the CS. The costs of AEs range substantially with the lowest being £702 for unspecified oedema and the highest £4,753 for acute myeloid leukemia. Costs are taken from the NHS reference costs 2021/22.

The costs for treatment-specific AEs are applied to all patients on treatment for the intervention and comparators.

Points for critique

The EAG notes that the model includes AE costs for patients off-treatment (whether progressed or not) when comparing avapritinib with 2L+ BAT, but this is not the case when comparing avapritinib with 1L midostaurin or 2L+ cladribine. The adverse event probabilities used to inform these costs are for cladribine implying that patients receive cladribine. The EAG believes this is a modelling error because it is not consistent with other parts of the model, e.g. there are no drug acquisition costs for subsequent treatment with cladribine or utility decrements associated with the AEs for cladribine. We have removed these costs from the EAG base case.

4.2.9.6 Treatment costs post progression or discontinuation

There are currently no subsequent treatment costs included in the model post progression or discontinuation.

Points for critique

As discussion previously, the EAG is concerned that there may be potential confounding of subsequent treatment effects on survival outcomes used in the model, but that the costs associated with the use of subsequent therapies (after discontinuation from initial treatment) are excluded from the model. Differential costs of subsequent therapy use for avapritinib and its comparators may represent a concern for the proportion of the cohort who receives allo-HSCT because the costs of the transplant are not included in the analysis.

The EAG also notes that the approach used in the CS deviates from TA728 where a one-off disease progression cost of £11,807 was included in the model to represent subsequent treatment costs with cladribine. In TA728, it was assumed that 50% of patients received a subsequent therapy.

4.2.9.7 End of life costs

In the model, the transition to the death state is associated with palliative care costs. These costs are informed by Round et al. 2015 [53], which estimates end-of-life palliative care costs for lung, breast, colorectal and prostate cancers in England and Wales across four categories: health care, social care, charity care, and informal care. The CS includes costs in the health and social care categories and these costs are averaged across the four cancer types and inflated to 2022/23. The total cost of palliative care is estimated to be £6,836.

Points for critique

The EAG considers the approach used by the company to be reasonable. The approach also aligns with that used in TA728, which used the same source and a very similar end-of-life palliative care cost of £7,797.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

The cost-effectiveness results presented in the CS are based on a confidential PAS discount for avapritinib, which was updated at EAG clarifications. A revised confidential PAS of [redacted]% of the list price of avapritinib is now included in the company's updated results in response to EAG clarifications. At clarifications, the company also revised the model and presented updated cost-effectiveness results in response to a number of modelling errors identified by the EAG (see Section 5.3). The EAG noted a further minor error in the model calculations since the response to clarifications, where the company had left in post-treatment adverse event costs for the comparison of avapritinib with 2L+ BAT (as proxy for cladribine) but no corresponding drug acquisition costs or

adverse event disutilities, whilst also excluding these costs for the other comparisons. The EAG has corrected this minor error for the company's updated cost-effectiveness results presented below, which had minimal impact on the results.

Table 21 shows the company's updated base case probabilistic and deterministic cost-effectiveness results for the three comparisons considered by the company:

- Comparison A: Avapritinib vs midostaurin, 1L
- Comparison B: Avapritinib vs BAT (as proxy for cladribine), 2L+
- Comparison C: Avapritinib vs cladribine, 2L+

The deterministic and probabilistic ICER for 1L avapritinib relative to 1L midostaurin is [redacted]. The deterministic ICER for avapritinib vs 2L+ BAT (as proxy for cladribine) is [redacted] and for avapritinib vs 2L+ cladribine is [redacted]. The corresponding probabilistic ICERs are [redacted] and [redacted], respectively. The cost effectiveness plane and acceptability curves are presented in Figure 9, 11 and 13 for the three comparisons. These show that the probability of avapritinib being cost-effective compared to 1L midostaurin, 2L+ BAT and 2L+ cladribine is [redacted], respectively, at cost-effectiveness thresholds of £20,000 and £30,000/QALY.

Table 21 Company's base case cost-effectiveness results (reproduced from Tables 22, 24, 25 and 26 from the company's clarification response).

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic analysis							
Comparison A: Avapritinib vs Midostaurin, 1L							
Midostaurin	[redacted]	3.24	2.03	-			
Avapritinib	[redacted]	6.11	4.31	[redacted]	2.86	2.27	[redacted]
Comparison B: Avapritinib vs BAT, 2L+							
Cladribine	[redacted]	3.07	1.58				
Avapritinib	[redacted]	4.85	2.90	[redacted]	1.78	1.33	[redacted]
Comparison C: Avapritinib vs cladribine, 2L+							
Cladribine	[redacted]	2.75	1.41	-			
Avapritinib	[redacted]	4.04	2.50	[redacted]	1.29	1.09	[redacted]
Probabilistic analysis							
Comparison A: Avapritinib vs Midostaurin, 1L							
Midostaurin	[redacted]		1.99				
Avapritinib	[redacted]		4.15	[redacted]		2.16	[redacted]
Comparison B: Avapritinib vs BAT, 2L+							
Cladribine	[redacted]		1.57				
Avapritinib	[redacted]		2.89	[redacted]		1.32	[redacted]
Comparison C: Avapritinib vs cladribine, 2L+							
Cladribine	[redacted]		1.42				
Avapritinib	[redacted]		2.48	[redacted]		1.07	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; BAT, best available therapy.

5.1.2 Points for critique

To aid understanding of the key drivers of the cost-effectiveness results, Table 22 and Table 23 provide a summary of the disaggregated costs and QALYs, respectively. The cost savings for avapritinib compared to midostaurin at 1L are predominantly driven by the difference in drug acquisition costs, with some of this cost offset by disease management costs. The difference in drug acquisition costs is also key to the differences in total costs for avapritinib compared with 2L cladribine and BAT (as proxy for cladribine). The QALY gain for avapritinib is driven by the improvements in HRQoL associated with remaining progression-free for longer relative to the comparators.

Table 22 Summary of the disaggregated costs in the company's deterministic base case results

Comparison A: Avapritinib vs Midostaurin, 1L				
Item	**Cost of Avapritinib 1L (£)**	**Cost of Midostaurin 1L (£)**	**Incremental costs (£)**	**% of total incremental costs**
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Comparison B: Avapritinib vs BAT, 2L+				
Item	**Cost of Avapritinib 2L+ (£)**	**Cost of BAT (£)**	**Incremental costs (£)**	**% of total incremental costs**
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Comparison C: Avapritinib vs cladribine 2L+				
Item	**Cost of Avapritinib 2L+ (£)**	**Cost of Cladribine (£)**	**Incremental costs (£)**	**% of total incremental costs**
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT, best available care.

Table 23 Summary of the disaggregated QALYs in the company's deterministic base case results

Comparison A: Avapritinib vs Midostaurin, 1L				
Item	**QALYs of Avapritinib 1L**	**QALYs of Avapritinib 2L+**	**Incremental QALYs**	**% of total incremental QALYs**
Progression free	3.70	1.04	2.66	87.41%
Progressed disease	0.61	0.99	-0.38	12.59%
Total	4.31	2.03	2.27	100%
Comparison B: Avapritinib vs BAT, 2L+				
Item	**QALYs of Avapritinib 2L+**	**QALYs of BAT 2L+**	**Incremental QALYs**	**% of total incremental QALYs**
Progression free	2.16	0.44	1.72	81.25%
Progressed disease	0.74	1.14	-0.4	18.75%
Total	2.90	1.58	1.33	100%
Comparison C: Avapritinib vs cladribine 2L+				
Item	**QALYs of Avapritinib 2L+**	**QALYs of Cladribine 2L+**	**Incremental QALYs**	**% of total incremental QALYs**
Progression free	2.08	0.39	1.68	74.38%
Progressed disease	0.42	1.02	-0.60	26.19%
Total	2.50	1.41	1.09	100%

Abbreviations: QALYs, quality-adjusted life years; BAT, best available treatment.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company reports univariate deterministic sensitivity analysis (DSA) via tornado plots of the ten most influential parameters (Figures 10, 12 and 14 of the company's response to clarifications). In the absence of confidence intervals or published ranges, upper and lower bounds tested in the DSA were calculated by assuming a standard error of 0.1. For all three comparisons, the results indicate that the most influential parameters on the ICER are age and the discount rate, while disease management costs from cycles 12+ are also important for the comparison of avapritinib versus 1L midostaurin, and cladribine administration costs and weight for the 2L+ population.

The original CS reports seventeen scenario analyses for avapritinib versus midostaurin, and sixteen scenario analyses for the 2L+ populations. The deterministic results are presented in tables 67, 68 and 69 of the CS. The company only reports that the ICER [redacted] under every scenario for the comparison of avapritinib versus 1L midostaurin. For the comparisons at 2L+, the scenario with the greatest impact on the cost-effectiveness results was from varying the duration of treatment benefit for avapritinib from 1 year to 10 years.

These scenarios were not updated in response to clarifications. However, the company did conduct three additional scenarios in response to EAG clarifications relating to the data sources and assumptions for duration of treatment and progression-free survival (tables 27, 28 and 29 of the company's response to EAG clarifications). The first scenario used duration of treatment from the PATHFINDER study instead of using real-world evidence. The second used the duration of treatment as a proxy for progression-free survival using real-world evidence and the third used duration of treatment as a proxy for progression-free survival but with data from the PATHFINDER study. Avapritinib [redacted] compared to 1L midostaurin across all three scenarios. The third scenario was the most influential on the comparisons at 2L+ with an increase in the baseline ICER of 83% and 52% (Comparison B and C).

No subgroup analyses were conducted by the company.

5.3 Model validation and face validity check

5.3.1 Summary of company's submission

The company undertook both clinical and technical validation of the model. Expert clinical input was sought to validate the model concept, the inputs and methods used, including the model structure, and assumptions.

For technical validation, the CS states quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. These procedures included verification of all input data with original sources, programme validation included checks of the model results, calculations, data references, model interface and visual basic for application code.

5.3.2 Points for critique

The EAG considers the company's stated validation procedure to be reasonable. However, the EAG reviewed the company model in detail and identified a number of errors. Firstly, the probabilistic simulations used to compute total costs and total QALYs, for avapritinib and comparators in rows 5-7 of worksheet 'PSA_data', varied with some computations based on 5,000 simulations and others 10,000 simulations. Secondly, cell D13 on worksheet 'QoL Data', was not referring to the correct progression-free utility for the comparison of avapritinib with cladribine. Thirdly, in the "LookUps" worksheet the "Setting_timetoHSCT" was linked to cell L154 rather than C154.

The company corrected these errors and resubmitted their model at EAG points for clarification. The EAG noticed a further error, namely the company had left in off-treatment adverse event costs when comparing avapritinib 2L+ versus BAT despite not including any corresponding post-treatment drug

acquisition costs or adverse event utilities. Correcting this made little difference to the results, but the results with this error corrected are provided above.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. A number of alternative scenarios are presented in areas where the EAG considers an alternative approach to be more appropriate than the company's updated base case analysis, or where it is considered important to explore the impact of uncertainty.

A description of the exploratory analyses is described in Section 6.1 and the impact of these analyses on the company's base case are presented in Sections 6.2. The EAG's preferred base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of avapritinib relative to 1L midostaurin and, separately, for avapritinib relative to 2L+ cladribine, or 2L+ BAT (proxy for cladribine). Where the EAG is unable to provide a judgement in the absence of evidence (e.g., longevity of the treatment benefits for avapritinib), the EAG have presented results of alternative scenarios to the EAG's preferred base case. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions and alternative scenarios to the EAG base case are presented in Section 6.3.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following exploratory analyses on the updated version of the company's model following EAG clarifications, with implementation of the corrections outlined in Section 5.

1. TOT sourced from PATHFINDER (avapritinib) and external cohort study (comparators)

As described in Section 4.2.6.2, TOT is a critical parameter in the model as it determines the duration of therapy and provides a proxy for PFS, which in turn drives treatment costs and duration of improved health-related quality of life benefits associated with PFS compared to PD. The EAG considers it more appropriate to source the TOT curve for avapritinib from PATHFINDER (safety population), adjusted for IPTW with the ECS, rather than the CUP in order to ensure consistency with the primary data source used to inform OS in the model and because of the limitations of the CUP data. The EAG also considers it more appropriate to use the IPTW sample from the ECS for the comparator's TOT rather than the unweighted median duration of therapy from the ECS in order to ensure comparability between the duration of therapy for avapritinib and the comparators.

Scenario 1 assesses the cost-effectiveness of avapritinib relative to 1L midostaurin, 2L+ cladribine and 2L+ BAT when TOT is sourced from the respective IPTW analysis from PATHFINDER (avapritinib) and the ECS (comparator).

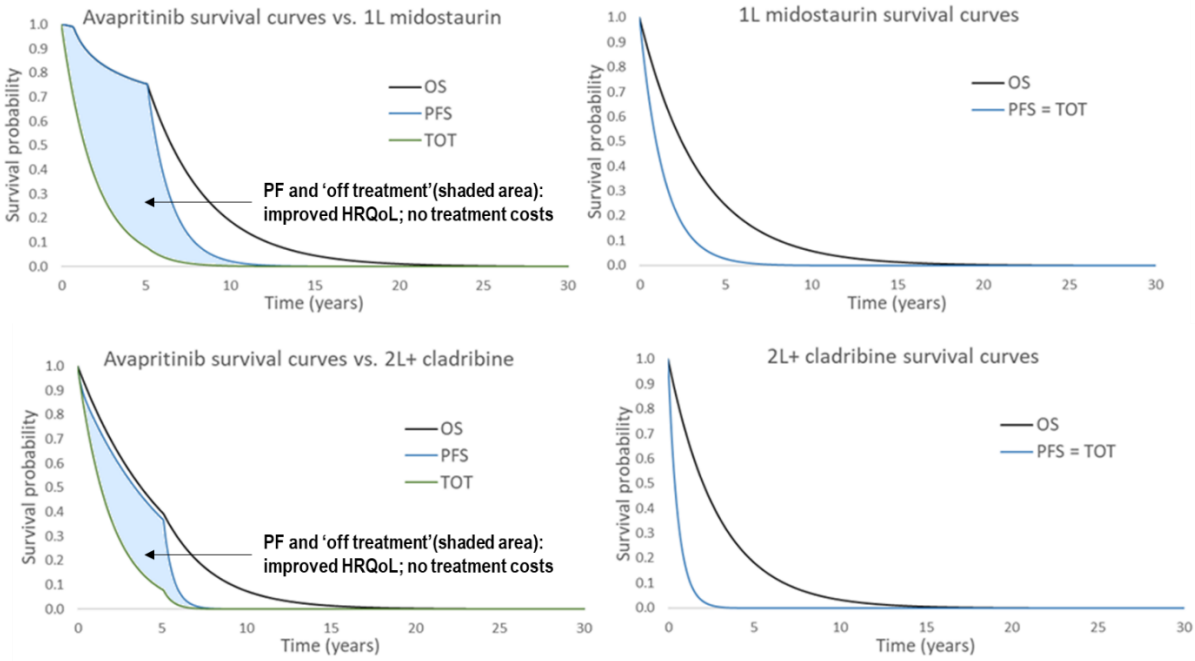
2. TOT as a proxy for PFS of avapritinib and sourced from PATHFINDER

As described in Section 4.2.6.2, one key difference between the modelled outcomes for avapritinib compared to the comparators in the company's base case is that a proportion of the cohort in the avapritinib arm have discontinued treatment before disease progression due to the application of separate TOT and PFS curves for avapritinib in the model, while for the comparators PFS is the same as TOT, i.e., the model assumes that patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression. This is illustrated in Figure 5 as the shaded area between the PFS and TOT curves for avapritinib, where avapritinib is modelled to have improved HRQoL compared to the comparators for patients who interrupt treatment before progression but with no treatment costs, while the comparator is not permitted to discontinue treatment before progression. The EAG considers it more appropriate to be consistent in the modelling approach used for avapritinib and the comparators and the EAG is not aware of reasons for discontinuing treatment with avapritinib before disease progression, which would not hold if the patient were treated with midostaurin or cladribine instead.

In Section 4.2.6.2, the EAG also expressed concerns that the PFS data from the RAC-RE population (unweighted analysis) of PATHFINDER is inconsistent with the OS data from the safety population (IPTW sample) of PATHFINDER used in the company's base case analysis. In particular, in the comparison of avapritinib with 1L midostaurin the treatment benefit from initiating treatment with avapritinib is maintained for a full 5 years without any disease progression (see Figure 5). The EAG considers this assumption to be unreasonable in light of the TOT curve used in the model for avapritinib. The implications of the unreasonable PFS data for avapritinib, when taken together with the inconsistent approach used for avapritinib PFS compared with midostaurin PFS (based on using TOT as a proxy for comparator PFS), is highly favouring the cost-effectiveness of avapritinib relative to 1L midostaurin. The EAG considers that the only reasonable approximation for PFS in the absence of alternative reliable estimates is to use the TOT curve as a proxy for PFS in both the avapritinib and comparator arms in the model, which ensures consistency across the intervention and comparators and ensures consistency with OS in the model when TOT is sourced from PATHFINDER (avapritinib).

Scenario 2 assesses the cost-effectiveness of avapritinib relative to 1L midostaurin, 2L+ cladribine and 2L+ BAT when the TOT curve is used as a proxy for PFS for both avapritinib and its comparator and TOT is sourced from the respective IPTW analysis from PATHFINDER (avapritinib) and the ECS (comparator).

Figure 5 Illustration of the shaded region between the PFS and TOT curves for avapritinib used in the company's base case analysis compared with 1L midostaurin and 2L+ cladribine, where avapritinib is modelled to have improved HRQoL and no treatment costs compared to the comparator.



3. OS extrapolations

As discussed in Section 4.2.6.2, the OS data used in the company's base case analysis from PATHFINDER at the September 2022 data cut-off is immature. Extrapolating the immature OS data beyond the limited follow-up of PATHFINDER using different parametric distributions leads to very different long-term survival outcomes; however, the extent to which the extrapolations have an impact on the cost-effectiveness results is constrained by the inclusion of a finite duration of treatment benefit of 5 years for avapritinib.

Given the immaturity of the OS data, the EAG considers four scenarios to explore uncertainty in the OS extrapolations when TOT is a proxy for PFS and sourced from IPTW analysis of PATHFINDER and ECS (i.e. Scenario 2), which the EAG considers to be the only reasonable approximation for PFS in the absence of suitable alternative data, while holding the duration of treatment effect for avapritinib of 5 years.

Scenarios 3a and 3b assess the impact on the cost-effectiveness of avapritinib relative to its comparators when the OS parametric extrapolation curves for avapritinib are based on the most pessimistic and most optimistic of the top three best fitted curves, respectively, while Scenarios 3c and 3d assess the impact when the OS parametric extrapolation curves for the comparator are based on the most pessimistic and most optimistic curves of the top three best fitted curves, respectively.

Importantly, the EAG notes that if the duration of avapritinib benefit is increased, the OS extrapolations will have a significant impact on the QALY gains associated with avapritinib. To further explore uncertainty in the OS extrapolations and the interplay with the duration of treatment benefit for avapritinib, several scenarios are outlined below under the duration of treatment benefit.

4. Duration of treatment benefit for avapritinib

As discussed in Section 4.2.6.2, the company assumed a 5-year treatment benefit for avapritinib relative to its comparators. The EAG considers the assumption of a 5-year treatment benefit for avapritinib to be reasonable in the 1L population; however, the EAG acknowledges that this could potentially be [redacted] when using the TOT curves from the IPTW analysis of PATHFINDER for avapritinib, where approximately [redacted] of patients remain on treatment at 5 years and progression-free (informed by TOT) in the comparison with 1L midostaurin (but lower in the comparisons with 2L+ cladribine and 2L+ BAT [redacted]).

To explore uncertainty associated with the longevity of the treatment effect for avapritinib and the potential impact of waning efficacy on cost-effectiveness, the EAG presents Scenarios 4-6 in which the duration of treatment effect is longer (more favourable to avapritinib) of 7.5 years, 10 years and lifetime, respectively, while holding the OS extrapolations the same as the company's base case and TOT the same as scenario 2.

Importantly, the EAG notes that there is an interplay between the survival outcomes in the model and the duration of treatment benefit assumed for avapritinib. Therefore, it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes assumed in the model. To further explore uncertainty between the survival extrapolations and the interplay with the duration of treatment benefit for avapritinib, the EAG presents scenarios for different durations of treatment effect when either a small or large treatment effect is assumed for the parametric survival extrapolations of OS and PFS=TOT (i.e., based on the most pessimistic or most optimistic extrapolations of the top three best fitted curves for OS and PFS). Under these scenarios, the impact on cost-effectiveness of avapritinib relative to its comparators is assessed as follows:

- Scenarios 7a and 7b for a small and large treatment effect for the parametric survival extrapolations, respectively, and a 5-year treatment benefit (base case duration);
- Scenarios 8a and 8b for a small and large treatment effect for the parametric survival extrapolations, respectively, and a 7.5-year treatment benefit;
- Scenarios 9a and 9b for a small and large treatment effect for the parametric survival extrapolations, respectively, and a 10-year treatment benefit;

- Scenarios 10a and 10b for a small and large treatment effect for the parametric survival extrapolations, respectively, and a lifetime treatment benefit.

5. Progression health state utility values

As discussed in Section 4.2.8.2, the utility values for the PF and PD health states are uncertain. The utility value for PF is applied for the total cohort progression-free over time. Due to the limitations of the mapped utility data from PATHFINDER, the EAG explores the impact of varying the PF utility value on the cost-effectiveness results, which also changes the PD utility value because the PD/PF utility ratio (also uncertain) is applied to the PF utility value.

Scenario 11 considers a small reduction in the PF utility value from [redacted] to [redacted] in the 1L population, and from [redacted] to [redacted] in the 2L+ population, in order to assess the sensitivity of the cost-effectiveness results to the utility values used in the model. In Scenario 11 the TOT curve is a proxy for PFS (Scenario 2), where no part of the cohort discontinues treatment before progression; therefore, the impact of the PF utility value on total QALYs for avapritinib is expected to be less than in the company's base case analysis, where a proportion of the cohort is assigned the PF utility value whilst off treatment.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 24, Table 25, and Table 26 show the results of the EAG scenarios for the comparisons of avapritinib with 1L midostaurin, 2L+ cladribine, and 2L+ BAT (proxy for cladribine), respectively.

For the 1L comparison with midostaurin, the [redacted]. [redacted]. EAG Scenario 1, where the TOT curves are sourced from the IPTW analysis from PATHFINDER and the ECS rather than the CUP for avapritinib and unweighted ECS for midostaurin, has a large impact on the company's base case results, where the [redacted]. EAG Scenario 2, which uses the TOT curve as a proxy for PFS for both avapritinib and the comparators, [redacted] reduces the incremental QALYs because no proportion of the avapritinib cohort discontinues treatment before disease progression as permitted in the company's base case. The EAG considers Scenario 2 to be the only reasonable approximation for PFS in the absence of alternative reliable estimates of PFS and ensures consistency with the assumption used for the comparator and also consistency with the OS estimates used in the model when TOT is sourced from the IPTW analysis. Therefore, the impact of all other scenarios is assessed in relation to EAG Scenario 2, which represents the EAG's preferred base case.

EAG Scenarios 3a-3d show that the incremental QALYs for the comparison of avapritinib with 1L midostaurin is highly sensitive to the OS extrapolation, with incremental QALYs ranging from 1.91 to 2.62 depending on choice of parametric curve extrapolation from the top three best fitted curves. For the 1L comparison, EAG Scenarios 4-6 show that the incremental QALYs [redacted] are highly dependent on the duration of treatment effect for avapritinib, where a longer duration of effect increases the QALYs significantly. EAG Scenarios 7-10 demonstrate the interplay between the duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered; the results show that [redacted] QALYs are highly sensitive to these assumptions, with EAG Scenario 10b providing the most optimistic case for avapritinib where both a lifetime duration of treatment effect is considered and a large treatment effect on the survival extrapolations. EAG Scenario 11 shows that the total QALYs are highly sensitive to the utility values used in the model, where a relatively small change in the PF utility value of [redacted] (corresponding to a change of [redacted] in the PD utility value) for the 1L comparison, results in a reduction in incremental total QALYs for avapritinib of 0.15 compared to the EAG's preferred base case (Scenario 2).

For the 2L+ comparisons of avapritinib with cladribine and BAT (proxy for cladribine), EAG Scenarios 1 and 2 have a large impact on the company's base case results, where the [redacted] As a result, the ICER change from the company's base case for Scenario 2 (which represents the EAG's preferred base case) is [redacted] and [redacted] for the comparisons with 2L+ cladribine and 2L+ BAT, respectively. EAG Scenarios 3a-3d show that the results are sensitive to the OS extrapolation, but that the company have been conservative in relation to the choice of OS extrapolation in the comparison of avapritinib with 2L+ cladribine. EAG Scenarios 4-6 show that the cost-effectiveness results in the 2L+ population are less sensitive to the duration of treatment therapy for avapritinib. This is because OS in the 2L+ population is considerably lower than in the 1L population; for example, approximately [redacted] of patients are alive at 7.5 years in the avapritinib arm ([redacted] in cladribine arm) and [redacted] alive at 10 years in the avapritinib arm ([redacted] in cladribine arm) for the comparison with 2L+ cladribine. EAG Scenarios 7a and 7b show that the cost-effectiveness results are highly sensitive to the joint parametric survival extrapolations used for OS and TOT in the comparison of avapritinib with 2L+ cladribine and, to a lesser extent, in the comparison with 2L+ BAT. As noted previously, the company has been more conservative in its selection of the parametric extrapolation curve for OS in the comparison with 2L+ cladribine. The interplay between the duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered (Scenarios 8-10) is less in the 2L+ population when the duration of treatment effect is greater than the base case of 5 years. EAG Scenario 11 shows that the total QALYs are highly sensitive to the utility values used in the model, where a relatively small change in the PF

utility value of [redacted] (corresponding to a change of [redacted] in the PD utility value) for the 2L+ population, results in a reduction in incremental total QALYs for avapritinib of 0.10 and 0.12 for the comparisons with 2L+ cladribine and 2L+ BAT, respectively, with corresponding ICER increase of [redacted] and [redacted], respectively, compared to the EAG's preferred base case (Scenario 2).

Table 24 Cost-effectiveness results of EAG scenarios – avapritinib vs 1L midostaurin

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company updated base case	Avapritinib	[redacted]	4.31	[redacted]	2.27	[redacted]
		Midostaurin	[redacted]	2.03			
1	Company updated base case + TOT sourced from PATHFINDER (avapritinib) and external cohort study (midostaurin)	Avapritinib	[redacted]	4.55	[redacted]	2.41	[redacted]
		Midostaurin	[redacted]	2.14			
2	EAG base case: TOT as proxy for PFS of avapritinib using PATHFINDER	Avapritinib	[redacted]	4.11	[redacted]	1.98	[redacted]
		Midostaurin	[redacted]	2.14			
3a	Pessimistic OS extrapolation for avapritinib: exponential (duration of TE of 5 years)	Avapritinib	[redacted]	4.04	[redacted]	1.91	[redacted]
		Midostaurin	[redacted]	2.14			
3b	Optimistic OS extrapolation for avapritinib: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	4.23	[redacted]	2.09	[redacted]
		Midostaurin	[redacted]	2.14			
3c	Pessimistic OS extrapolation for midostaurin: exponential (similar extrapolation to the company's base case) (duration of TE of 5 years)	Avapritinib	[redacted]	4.11	[redacted]	1.98	[redacted]
		Midostaurin	[redacted]	2.14			
3d	Optimistic OS extrapolation for midostaurin: log logistic (duration of TE of 5 years)	Avapritinib	[redacted]	5.02	[redacted]	2.62	[redacted]
		Midostaurin	[redacted]	2.40			
4	EAG base case + duration of TE of 7.5 years	Avapritinib	[redacted]	4.78	[redacted]	2.64	[redacted]
		Midostaurin	[redacted]	2.14			
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	5.32	[redacted]	3.18	[redacted]
		Midostaurin	[redacted]	2.14			
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	6.46	[redacted]	4.32	[redacted]

		Midostaurin	[redacted]	2.14			
7a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic TOT avapritinib (exponential) + optimistic TOT midostaurin (generalised gamma) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.97	[redacted]	2.55	[redacted]
		Midostaurin	[redacted]	2.42			
7b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (log normal) Large TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.25	[redacted]	2.11	[redacted]
		Midostaurin	[redacted]	2.14			
8a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic TOT avapritinib (exponential) + optimistic TOT midostaurin (generalised gamma) Small TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	5.43	[redacted]	3.00	[redacted]
		Midostaurin	[redacted]	2.42			
8b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (log normal) Large TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.99	[redacted]	2.85	[redacted]
		Midostaurin	[redacted]	2.14			
9a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic TOT avapritinib (exponential) + optimistic TOT midostaurin (generalised gamma) Small TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	5.64	[redacted]	3.22	[redacted]
		Midostaurin	[redacted]	2.42			
9b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (log normal) Large TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	5.58	[redacted]	3.44	[redacted]
		Midostaurin	[redacted]	2.14			
10a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic TOT avapritinib (exponential) + optimistic TOT midostaurin (generalised gamma) Small TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	5.77	[redacted]	3.34	[redacted]
		Midostaurin	[redacted]	2.43			
10b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (log normal) Large TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	6.85	[redacted]	4.71	[redacted]
		Midostaurin	[redacted]	2.14			
11	EAG base case + PF utility of 0.7	Avapritinib	[redacted]	3.82	[redacted]	1.83	[redacted]
		Midostaurin	[redacted]	1.98			

OS, overall survival; TOT, time on treatment; TE, treatment effect; PF, progression-free; EAG, external assessment group

Table 25 Cost-effectiveness results of EAG scenario - avapritinib vs 2L+ cladribine

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company updated base case	Avapritinib	[redacted]	2.50	[redacted]	1.09	[redacted]
		Cladribine	[redacted]	1.41			
1	Company updated base case + TOT sourced from PATHFINDER (avapritinib) and external cohort study (cladribine)	Avapritinib	[redacted]	2.49	[redacted]	1.10	[redacted]
		Cladribine	[redacted]	1.40			
2	EAG base case: TOT as proxy for PFS of avapritinib using PATHFINDER	Avapritinib	[redacted]	2.40	[redacted]	1.01	[redacted]
		Cladribine	[redacted]	1.40			
3a	Pessimistic OS extrapolation for avapritinib: exponential (similar extrapolation to the company's base case) (duration of TE of 5 years)	Avapritinib	[redacted]	2.40	[redacted]	1.01	[redacted]
		Cladribine	[redacted]	1.40			
3b	Optimistic OS extrapolation for avapritinib: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	2.51	[redacted]	1.11	[redacted]
		Cladribine	[redacted]	1.40			
3c	Pessimistic OS extrapolation for cladribine: log normal (duration of TE of 5 years)	Avapritinib	[redacted]	3.13	[redacted]	1.21	[redacted]
		Cladribine	[redacted]	1.92			
3d	Optimistic OS extrapolation for cladribine: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	3.44	[redacted]	1.39	[redacted]
		Cladribine	[redacted]	2.05			
4	EAG base case + duration of TE of 7.5 years	Avapritinib	[redacted]	2.63	[redacted]	1.24	[redacted]
		Cladribine	[redacted]	1.40			
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	2.77	[redacted]	1.37	[redacted]

		Cladribine	[redacted]	1.40			
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	2.95	[redacted]	1.55	[redacted]
		Cladribine	[redacted]	1.40			
7a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	3.41	[redacted]	1.36	[redacted]
		Cladribine	[redacted]	2.05			
7b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	3.37	[redacted]	1.44	[redacted]
		Cladribine	[redacted]	1.92			
8a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.13	[redacted]	1.08	[redacted]
		Cladribine	[redacted]	2.05			
8b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.57	[redacted]	1.65	[redacted]
		Cladribine	[redacted]	1.93			
9a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	2.91	[redacted]	0.86	[redacted]
		Cladribine	[redacted]	2.05			
9b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	3.75	[redacted]	1.82	[redacted]
		Cladribine	[redacted]	1.93			
10a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	2.72	[redacted]	0.69	[redacted]
		Cladribine	[redacted]	2.02			
10b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	4.17	[redacted]	2.24	[redacted]
		Cladribine	[redacted]	1.93			
11	EAG base case + PF utility of 0.6	Avapritinib	[redacted]	2.16	[redacted]	0.90	[redacted]
		Cladribine	[redacted]	1.25			

OS, overall survival; TOT, time on treatment; TE, treatment effect; PF, progression-free; EAG, external assessment group

Table 26 Cost-effectiveness results of EAG scenario - avapritinib vs 2L+ BAT

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company updated base case	Avapritinib	[redacted]	2.90	[redacted]	1.33	[redacted]
		BAT	[redacted]	1.58	-		
1	Company updated base case + TOT sourced from PATHFINDER (avapritinib) and external cohort study (BAT)	Avapritinib	[redacted]	3.13	[redacted]	1.47	[redacted]
		BAT	[redacted]	1.66	-		
2	EAG base case: TOT as proxy for PFS of avapritinib using PATHFINDER	Avapritinib	[redacted]	2.87	[redacted]	1.21	[redacted]
		BAT	[redacted]	1.66	-		
3a	Pessimistic OS extrapolation for avapritinib: gamma (duration of TE of 5 years)	Avapritinib	[redacted]	2.81	[redacted]	1.15	[redacted]
		BAT	[redacted]	1.66	-		
3b	Optimistic OS extrapolation for avapritinib: log logistic (duration of TE of 5 years)	Avapritinib	[redacted]	2.89	[redacted]	1.23	[redacted]
		BAT	[redacted]	1.66	-		
3c	Pessimistic OS extrapolation for BAT: Weibull (similar extrapolation to the company's base case) (duration of TE of 5 years)	Avapritinib	[redacted]	2.87	[redacted]	1.21	[redacted]
		BAT	[redacted]	1.66	-		
3d	Optimistic OS extrapolation for BAT: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	3.61	[redacted]	1.67	[redacted]
		BAT	[redacted]	1.94	-		
4	EAG base case + duration of TE of 7.5 years	Avapritinib	[redacted]	2.97	[redacted]	1.31	[redacted]
		BAT	[redacted]	1.66	-		
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	3.03	[redacted]	1.36	[redacted]
		BAT	[redacted]	1.66	-		
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	3.08	[redacted]	1.42	[redacted]

		BAT	[redacted]	1.66	-		
7a	Pessimistic OS avapritinib (gamma) + optimistic OS BAT (Gompertz) Pessimistic TOT avapritinib (log normal) + optimistic TOT BAT (Gompertz) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	3.50	[redacted]	1.57	[redacted]
		BAT	[redacted]	1.94	-		
7b	Optimistic OS avapritinib (log logistic) + pessimistic OS BAT (Weibull) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT BAT (log normal) Large TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	2.99	[redacted]	1.29	[redacted]
		BAT	[redacted]	1.70	-		
8a	Pessimistic OS avapritinib (gamma) + optimistic OS BAT (Gompertz) Pessimistic TOT avapritinib (log normal) + optimistic TOT BAT (Gompertz) Small TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.34	[redacted]	1.40	[redacted]
		BAT	[redacted]	1.94	-		
8b	Optimistic OS avapritinib (log logistic) + pessimistic OS BAT (Weibull) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT BAT (log normal) Large TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.25	[redacted]	1.55	[redacted]
		BAT	[redacted]	1.70	-		
9a	Pessimistic OS avapritinib (gamma) + optimistic OS BAT (Gompertz) Pessimistic TOT avapritinib (log normal) + optimistic TOT BAT (Gompertz) Small TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	3.15	[redacted]	1.21	[redacted]
		BAT	[redacted]	1.94	-		
9b	Optimistic OS avapritinib (log logistic) + pessimistic OS BAT (Weibull) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT BAT (log normal) Large TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	3.42	[redacted]	1.72	[redacted]
		BAT	[redacted]	1.70	-		
10a	Pessimistic OS avapritinib (gamma) + optimistic OS BAT (Gompertz) Pessimistic TOT avapritinib (log normal) + optimistic TOT BAT (Gompertz) Small TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	2.88	[redacted]	0.97	[redacted]
		BAT	[redacted]	1.91	-		
10b	Optimistic OS avapritinib (log logistic) + pessimistic OS BAT (Weibull) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT BAT (log normal) Large TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	3.77	[redacted]	2.07	[redacted]
		BAT	[redacted]	1.70	-		
11	EAG base case + PF utility of 0.6	Avapritinib	[redacted]	2.57	[redacted]	1.08	[redacted]
		BAT	[redacted]	1.49	-		

OS, overall survival; TOT, time on treatment; TE, treatment effect; PF, progression-free; EAG, external assessment group; BAT, best available therapy.

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes to the company's base case:

- TOT for avapritinib is sourced from PATHFINDER (rather than CUP), adjusted for IPTW with the ECS, and TOT for the comparators is sourced from the IPTW analysis of ECS (rather than unweighted ECS) – Scenario 1;
- TOT is a proxy for PFS for both avapritinib and the comparators (rather than comparators only) and sourced from IPTW analysis of PATHFINDER and ECS – Scenario 2 (includes Scenario 1).

The results of Scenario 2 in Section 6.2 show the cumulative impact of the EAG's preferred assumptions on the ICER.

The EAG's preferred base case is based on the evidence currently available; notably the September 2022 data cut-off of PATHFINDER, i.e., not the most recent data cut-off of September 2023 because this data has not yet been made available to the EAG by the company.

A number of important uncertainties remain, which cannot be adequately addressed with the available evidence:

- Immaturity of the OS data used in the extrapolations and the potential confounding effects of prior midostaurin use on OS in the 2L+ population;
- Immaturity of PFS data from PATHFINDER and lack of PFS data for the comparators;
- Uncertainty about the duration of treatment benefit for avapritinib relative to the comparators;
- Impact of subsequent therapies on survival outcomes after discontinuation from initial treatment, and post-progression costs and utility values; and
- Uncertainty about the PF and PD health state utility values.

Table 27, Table 28, and Table 29 summarise the results of the EAG's preferred base case for the comparison with 1L midostaurin, 2L+ cladribine, and 2L+ BAT (proxy for cladribine), respectively.

Table 27 EAG's preferred base case for the comparison of avapritinib with 1L midostaurin

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	2.27	[redacted]
EAG's preferred base case	[redacted]	1.98	[redacted]

Table 28 EAG's preferred base case for the comparison of avapritinib with 2L+ cladribine

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	1.09	[redacted]
EAG's preferred base case	[redacted]	1.01	[redacted]

Table 29 EAG's preferred base case for the comparison of avapritinib with 2L+ BAT

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	1.33	[redacted]
EAG's preferred base case	[redacted]	1.21	[redacted]

6.4 Conclusions of the cost effectiveness section

The company submitted a partitioned survival analysis to compare the cost-effectiveness of avapritinib with midostaurin in adult patients with AdvSM who have not received prior systemic therapies (1L population), and avapritinib compared with cladribine in adult patients with AdvSM who have received prior systemic therapies (2L+ population). The company also compared avapritinib with BAT consisting of a mixture of therapies, including midostaurin and cladribine, in the 2L+ population, which was considered by the company to be an exploratory analysis as a proxy for 2L+ cladribine. Subpopulations by disease subtype (ASM, SM-AHN and MCL) are not considered in the economic analysis. The EAG's primary concern in relation to the population included in the cost-effectiveness assessment is the limited justification for the separation of the population by treatment line, which implies that a separate recommendation for avapritinib is required in those who have received prior systemic therapies (2L+ population) from those who have not (1L population), whereas the NICE recommendation for midostaurin is not restricted to the 1L population. The EAG considers that the separation of the population by treatment line has resulted in treatment comparisons that are determined by increasing the sample size due to the immaturity of the available survival data (e.g., including a larger cohort of 2L+ BAT, which consists of therapies that may not be applicable to the NHS since the introduction of midostaurin) rather than reflecting the likely treatment pathway for AdvSM in the UK. The EAG believes that there is merit in assessing the cost-effectiveness of avapritinib compared with midostaurin in the overall population, i.e., not separated by line of treatment. This would involve using data from the entire ECS for midostaurin, who had received ≥1 line of systemic therapy (not necessarily as 1L) for AdvSM and data for avapritinib from

PATHFINDER (and/or combined with EXPLORER 200 mg OD), with an adjustment made to balance for differences in treatment lines using the propensity weights, which also avoids discarding data by prior use of systemic therapies that is necessary when splitting the data by treatment line.

The company's base case model structure is consistent with the model structure used in TA728 (midostaurin), which was considered by the Appraisal Committee to be suitable for decision making. The model includes four elements relating to treatment effectiveness and extrapolation of effects over time, by treatment initiated: OS, PFS, TOT, and duration of treatment benefit for avapritinib. The main limitation of the extrapolated OS in the company's base case analysis is that it is estimated independent of PFS and other intermediate endpoints such as treatment response rates. The company's model does not consider survival outcomes for separate clinical events such as those for individuals with PD and pre- or post-progression deaths, which is likely to be affected by subsequent treatment use after discontinuation from the primary treatment. The EAG has a number of major concerns in relation to the treatment effectiveness evidence used in the model and the assumptions, which are likely to favour the cost-effectiveness of avapritinib relative to the comparators and increase uncertainty in the two separate populations. The first concern relates to the lack of consistency in the sources of data used to inform the different survival parameters and duration of therapy, whereby the company uses the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW for the comparisons with the relevant comparators in the 1L and 2L+ populations, but uses the RAC-RE population unweighted analysis for PFS for avapritinib. More importantly, TOT for avapritinib, which determines the time until treatment discontinuation due to disease progression or other reasons, is not informed by PATHFINDER and is therefore not consistent with the PFS and OS outcomes used in the model. Furthermore, the approach used to determine the probability of moving to the progressive disease health state, via the PFS and OS curves, differs for avapritinib and the comparators, where the TOT curve is used as a proxy for PFS for the comparators but not for avapritinib. This mismatch of different sources of evidence to inform inter-related parameters in the model (PFS, TOT and OS) is a major concern because it creates inconsistencies in the data used. The second concern relates to the immaturity of the OS data used in the extrapolations and the potential confounding effects of prior midostaurin use on OS in the 2L+ population. The EAG is particularly concerned about the accuracy of the substantial OS benefit for avapritinib compared to 1L midostaurin, which only falls at 5 years because of the assumed duration of treatment benefit. The third concern relates to the limited availability of PFS data, which was not available from the ECS and the PFS data from the RAC-RE population (unweighted analysis) of PATHFINDER is inconsistent with the OS data from the safety population (IPTW sample) of PATHFINDER. The company uses the comparator's TOT curve as a proxy for the comparator's PFS curve, but not for avapritinib. As a result, patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression, whereas avapritinib is modelled to

receive QALY gains for patients who interrupt treatment before progression, with no treatment costs after discontinuation. A fourth concern is that TOT for avapritinib is sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the CUP, which is not consistent with the OS outcomes used in the model, not separated by treatment line as required by the model, and only median duration of therapy is available from CUP. A fifth concern is the lack of evidence for the duration of treatment effect for avapritinib, which is assumed to be 5 years in the model. The EAG notes that it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes assumed in the model when assessing the cost-effectiveness of avapritinib relative to its comparators because if the OS extrapolation based on immature data is highly optimistic, then an appropriate cap on the duration of treatment benefit is required. A sixth concern relates to the impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment, which is not considered in the company's base case analysis in the 1L or 2L+ populations. The EAG is concerned that there may be potential confounding of subsequent treatment effects on survival outcomes reported in PATHFINDER for avapritinib, but that the costs (and utility values) associated with the use of subsequent therapies are excluded from the model. A further concern relates to uncertainty in the utility values for the PF and PD health states of the model, where there are limited numbers of observations at each time point in the PATHFINDER study to inform the mapped utility value associated with PF in the 1L and 2L+ populations, and an absence of data post-progression.

The modelled assumptions with the largest impact on the ICER are those relating to:

- The OS extrapolation that affects the magnitude of the OS benefit for avapritinib relative to its comparators, which is substantial for avapritinib compared to 1L midostaurin (and only falls at 5 years because of the duration of treatment benefit assumption). In comparison, the OS benefit for avapritinib compared to 2L+ cladribine or BAT is substantially smaller than avapritinib compared to midostaurin, which, when taken at face value, goes against the intuition of expecting to observe greater survival benefit for avapritinib compared to cladribine because cladribine is a less effective treatment option for AdvSM compared to midostaurin.
- The duration of treatment survival benefit for avapritinib of 5 years, which is greater than the 3-year midostaurin treatment benefit in TA728. Importantly, there is an interplay between the survival outcomes and the duration of treatment benefit assumed for avapritinib on the ICER results. The results show that [redacted] QALYs are highly sensitive to the assumptions about OS extrapolation and duration of benefit.
- The source of evidence used to inform TOT because the duration of therapy for avapritinib from PATHFINDER, adjusted for IPTW with the ECS, is longer compared to the median duration from the small cohort of patients in CUP. This has a large impact on the company's

base case results, where the [redacted] for avapritinib relative to its comparators.

- TOT curves as a proxy for PFS for both avapritinib and the comparators because in the company's base case a proportion of the avapritinib cohort could discontinue treatment before disease progression, while no part of the cohort for comparators could discontinue treatment before progression. This [redacted] reduces the incremental QALYs for avapritinib relative to its comparators.
- The utility values for PF and PD health states, where the total QALYs are highly sensitive to the utility values used in the model.

The EAG's preferred assumptions include the following changes to the company's base case: (i) TOT for avapritinib is sourced from PATHFINDER (rather than CUP), adjusted for IPTW with the ECS, and TOT for the comparators is sourced from the IPTW analysis of ECS (rather than unweighted ECS); and (ii) TOT is a proxy for PFS for both avapritinib and the comparators (rather than comparators only) and sourced from IPTW analysis of PATHFINDER and ECS. However, the EAG considers that a number of important uncertainties remain, which cannot be adequately addressed with the available evidence: (i) immaturity of the OS data; (ii) immaturity of PFS data from PATHFINDER and lack of PFS data for the comparators; (iii) uncertainty about the duration of treatment benefit for avapritinib relative to its comparators; (iv) the impact of subsequent therapies on survival outcomes after discontinuation from initial treatment, and post-progression costs and utility values; and (v) uncertainty about the PF and PD health state utility values.

7 SEVERITY MODIFIER

7.1 Summary of company's submission

The CS provides the results of four QALY shortfall analyses using different sources for starting age and percentage of females (method 1, 2 and 3), or using QALYs extracted from TA728 (method 4). The results of the first three methods are split by treatment line, while the fourth considers all AdvSM patients. Method 4 cannot provide results for the comparison of avapritinib with 1L midostaurin and for the comparison with 2L+ cladribine or BAT, the QALYs for midostaurin are redacted. Table 30 summarises the starting age and gender distribution used in each method.

Table 30 Sources of population characteristics used in the company's QALY shortfall analysis

	Starting age		% of females		Sources
	1L	2L+	1L	2L+	
Method 1	68	67	47%	39%	PATHFINDER
Method 2	52	52	54%	54%	Skriskandarajah et al., 2021[14]
Method 3	62	62	47%	39%	Sperr et al., 2019[2] for starting age PATHFINDER for gender distribution
Method 4	63		36%		TA728[23]

The CS states that patients with AdvSM fail to meet the absolute or proportional shortfall criteria in the 1L or 2L+ populations using the company's base case model (method 1). However, the EAG identified two major errors in the electronic version of the model, which had a substantial impact on the QALY shortfall for the 2L+ population:

- For the comparison with cladribine, the PF health state utility value was incorrectly linked to the value of for the 1L population; and
- For the comparison with BAT (as a proxy for cladribine), the model incorrectly utilised an exponential parametric distribution for OS instead of a Weibull distribution, which was assessed by the company as the most appropriate parametric distribution for OS of BAT.

The company corrected these errors during the clarification stage but did not provide results of the updated QALY shortfall analysis. The EAG provides the results of the QALY shortfall analysis using the company's updated base case model in Table 31. Patients with AdvSM meet the proportional shortfall criteria in the 2L+ population, at the QALY weight of 1.2, based on the company's base case (method 1). The updated QALYs in the 2L+ population in methods 2 and 3 do not change.

Table 31 Updated company's QALY shortfall analysis (method 1)

	Company updated base case			Reference case from QALY shortfall calculator (Schneider et al. 2023)[54]			
Setting	Start age	% of females	QALYs on SoC (output from model)	QALYs for general population	Absolute QALY shortfall	Proportional QALY shortfall	NICE severity weighting
1L MIDO	68	47%	2.03	9.87	7.84	0.79	1.0
2L+ CLAD	67	39%	1.41	10.20	8.79	0.86	1.2
2L+ BAT	67	39%	1.58	10.20	8.62	0.85	1.2

QALY, quality adjusted life year; SoC, standard of care; BAT, best available therapy.

7.2 Points for critique

The EAG has major concerns regarding the suitability of methods 2, 3, and 4 for accurately reflecting the health outcomes of patients with AdvSM under current standard of care in UK practice. Methods 2 and 3 diverge from method 1 primarily by altering the starting age and gender distributions, resulting in a younger population overall. Implicit in these methods is the assumption that the survival outcomes and health state utility values remain consistent across age groups. The EAG considers that this assumption is very unlikely to hold. While clinical advice to both the company and the EAG suggests that patients in the PATHFINDER trial (method 1) may be slightly older (median age: 68 [range: 39, 88]) compared to the average age seen in UK practice, the EAG is unable to assess the impact of a younger population on the QALY shortfall because this would require survival outcomes and health state utility values for the younger age population that is not available.

The EAG also considers method 4 unsuitable for decision making. This method directly extracts QALYs for BAT from TA728.[23] However, the EAG believes that the QALYs derived from BAT in TA728 are irrelevant for the current assessment as they do not reflect the altered treatment landscape since the publication of TA728, with the introduction of midostaurin, which is most commonly used in UK practice. Therefore, method 1 (i.e., using the company's model with the base line characteristics from PATHFINDER) is the most appropriate to estimate the health outcomes of patients with AdvSM undergoing the standard of care treatment in the UK.

In Section 6.3, the EAG presents their preferred base case assumptions that differ from the company's base case. The EAG indicates a preference for using TOT as a proxy for PFS for both avapritinib and the comparators to ensure consistency across the treatments. In addition, the EAG considers the source of TOT should come from PATHFINDER (rather than CUP), adjusted for IPTW with the ECS, and TOT for the comparators is sourced from the IPTW analysis of ECS (rather than unweighted ECS) to ensure consistency with OS used in the model. The EAG's preferred base case assumptions have implications for the total QALYs for the comparators, thus affecting the results of the QALY shortfall analysis. Table 32 shows the EAG additional analyses for the QALY shortfall reflecting the EAG's preferred base case (using method 1). The criteria for including a severity weighting is only met for the 2L+ population with cladribine as the comparator, while it is borderline for the comparison with 2L+ BAT (proxy for cladribine).

The EAG concludes that only the population in 2L+ with cladribine meets the NICE criteria for severity weighting, and the QALY weight is 1.2.

Table 32 EAG base case QALY shortfall analysis

	EAG base case			Reference case from QALY shortfall calculator (Schneider et al. 2023)[54]			
	Start age	**% of females**	**QALYs on SoC (output from model)**	**QALYs for general population**	**Absolute QALY shortfall**	**Proportional QALY shortfall**	**NICE severity weighting**
1L MIDO	68	47%	2.14	9.87	7.73	0.78	1.0
2L+ CLAD	67	39%	1.41	10.20	8.80	0.86	1.2
2L+ BAT	67	39%	1.66	10.20	8.54	0.84	1.0

QALY, quality adjusted life year; SoC, standard of care; BAT, best available therapy.

Table 33 presents the corresponding cost-effectiveness results for the EAG scenarios, using a severity weight of 1.2 for the QALYs of avapritinib compared to 2L+ cladribine.

Table 33 Cost-effectiveness results of EAG scenario - avapritinib vs 2L+ cladribine– severity weighting of 1.2 applied to avapritinib's QALYs

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company updated base case	Avapritinib	[redacted]	3.00	[redacted]	1.59	[redacted]
		Cladribine	[redacted]	1.41			
1	Company updated base case + TOT sourced from PATHFINDER (avapritinib) and external cohort study (cladribine)	Avapritinib	[redacted]	2.99	[redacted]	1.60	[redacted]
		Cladribine	[redacted]	1.40			
2	EAG base case: TOT as proxy for PFS of avapritinib using PATHFINDER	Avapritinib	[redacted]	2.88	[redacted]	1.49	[redacted]
		Cladribine	[redacted]	1.40			
3a	Pessimistic OS extrapolation for avapritinib: exponential (similar extrapolation to the company's base case) (duration of TE of 5 years)	Avapritinib	[redacted]	2.88	[redacted]	1.49	[redacted]
		Cladribine	[redacted]	1.40			
3b	Optimistic OS extrapolation for avapritinib: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	3.01	[redacted]	1.62	[redacted]
		Cladribine	[redacted]	1.40			
3c	Pessimistic OS extrapolation for cladribine: log normal (duration of TE of 5 years)	Avapritinib	[redacted]	3.76	[redacted]	1.83	[redacted]
		Cladribine	[redacted]	1.92			
3d	Optimistic OS extrapolation for cladribine: Gompertz (duration of TE of 5 years)	Avapritinib	[redacted]	4.13	[redacted]	2.08	[redacted]
		Cladribine	[redacted]	2.05			
4	EAG base case + duration of TE of 7.5 years	Avapritinib	[redacted]	3.16	[redacted]	1.77	[redacted]
		Cladribine	[redacted]	1.40			
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	3.32	[redacted]	1.92	[redacted]
		Cladribine	[redacted]	1.40			
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	3.53	[redacted]	2.14	[redacted]
		Cladribine	[redacted]	1.40			
7a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.09	[redacted]	2.04	[redacted]
		Cladribine	[redacted]	2.05			

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
7b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.04	[redacted]	2.12	[redacted]
		Cladribine	[redacted]	1.92			
8a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.75	[redacted]	1.70	[redacted]
		Cladribine	[redacted]	2.05			
8b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.29	[redacted]	2.36	[redacted]
		Cladribine	[redacted]	1.93			
9a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	3.49	[redacted]	1.45	[redacted]
		Cladribine	[redacted]	2.05			
9b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	4.50	[redacted]	2.57	[redacted]
		Cladribine	[redacted]	1.93			
10a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (exponential) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	3.26	[redacted]	1.24	[redacted]
		Cladribine	[redacted]	2.02			
10b	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (log normal) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	5.00	[redacted]	3.07	[redacted]
		Cladribine	[redacted]	1.93			
11	EAG base case + PF utility of 0.6	Avapritinib	[redacted]	2.59	[redacted]	1.34	[redacted]
		Cladribine	[redacted]	1.25			

OS, overall survival; TOT, time on treatment; TE, treatment effect; PFS, progression-free survival; EAG, external assessment group.

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APPENDICES

APPENDIX 1. EAG APPRAISAL OF EVIDENCE IDENTIFICATION

Table 34 EAG appraisal of clinical effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	The documentation was mostly clear and comprehensive. In the CS, the update searches of the Cochrane Library databases appeared to have been conducted via Wiley rather than Ovid as listed. This was raised as a clarification question and the company confirmed that Wiley had been used. In the CS, there were inconsistencies in the reporting of the number of studies/reports included between the CS, Section B.2.1 and the PRISMA diagram in Figure 1, Appendix D. This was raised as a clarification question. In response, the company clarified that 32 studies with 79 publications were included. The company also clarified the number of individual studies from the 7 reports included from the update review as shown in the PRISMA diagram in Figure 2, Appendix D.
Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases was used. However, although HTA sources were searched, no up-to-date HTA databases were searched. As real world evidence was part of the inclusion criteria, the EAG asked whether any relevant evidence could have been found in the following sources: the Central Data Registry of The European Competence Network on Mastocytosis (https://innere-med-1.meduniwien.ac.at/en/unsere-klinischen-abteilungen/haematologie-und-haemostaseologie/projekte/ecnm-the-european-competence-network-mastocytosis/ecnm-registry/) and the EMA's catalogue of RWD sources (https://catalogues.ema.europa.eu/catalogue-rwd-sources). The company responded that one additional relevant result was found searching these resources, which could not be accessed.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was for the update searches.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	The searches combined the condition with the interventions. There were no search terms for the comparators listed in the inclusion criteria, which was raised as a clarification question. The company responded that 'Adding comparator terms would have excluded additional papers' but this is incorrect. Although using the Boolean operator 'AND' would have excluded additional papers, using the Boolean operator 'OR' would have increased the number of hits overall. As an example, one of the comparators was best supportive care. The company could have searched for the condition with either the interventions or the comparators: Condition AND (Intervention OR Comparator).
Were appropriate search terms used?	PARTLY	Search terms for the condition and intervention were comprehensive. However, there were no search terms for the comparators listed in the inclusion criteria, as described above. As the company were incorrect in their statement that 'Adding comparator terms would have excluded additional papers' records including terms for comparators would have been missed if they did not also feature one of the intervention terms.

		There were a couple of missed condition terms, e.g. mast cell disease(s) and mastocytoses. However, this is unlikely to have made much difference to the literature. It would have been better if intervention terms were truncated in the strategies to pick up drug names with ® at the end (or other symbols). Similarly, where possible, it would have been better to search for the interventions with a wider range of field codes, as there are some for drugs and trade names on Ovid databases. Otherwise, it is a bit misleading to explode subject headings on databases where there are no nested terms.
Were any search restrictions applied appropriate?	YES	Yes, animal studies and irrelevant paper types were removed appropriately.
Were any search filters used, validated and referenced?	NO	Filters were not used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. EAG APPRAISAL OF COST-EFFECTIVENESS EVIDENCE IDENTIFICATION

The original company submission included searches to identify cost-effectiveness studies for adult patients with advanced systemic mastocytosis. A description of the searches and all the search strategies were included in Appendix G (pp. 67-83).

In response to the EAG's points for clarification the company provided additional information and corrections to errors identified by the EAG.

Table 35 EAG appraisal of cost-effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	The documentation is clear and comprehensive. In the original company submission, the update searches of the Cochrane library databases appeared to have been conducted via Wiley rather than Ovid as listed. This was raised as a clarification question and the company confirmed that Wiley had been used.
Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, and grey literature sources and were searched.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was for the update searches.

Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive. There were a couple of missed condition terms, e.g. mast-cell disease(s) and mastocytoses. However, this is unlikely to have made much difference to the literature.
Were any search restrictions applied appropriate?	N/A	There were no search restrictions applied.
Were any search filters used validated and referenced?	UNCLEAR	There were no references for search filters.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 3. EAG APPRAISAL OF HEALTH-RELATED QUALITY OF LIFE EVIDENCE IDENTIFICATION

The original company submission included searches to identify health-related quality of life studies for adult patients with advanced systemic mastocytosis. A description of the searches and all the search strategies were included in Appendix H (pp. 86-104).

In response to the EAG's points for clarification the company provided additional information and corrections to errors identified by the EAG.

Table 36 EAG appraisal of health-related quality of life evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	The documentation is mostly clear and comprehensive. However, the description of how the health-related quality of life studies were performed was not included in the original company submission, which was raised as a clarification question. The company responded with the page number of the description of the searches. Although the description section does contain text, the text is sentences such as 'Describe how systematic searches for relevant health-related quality-of-life data were done' and there is no actual description. In the original company submission, the update searches of the Cochrane library databases appeared to have been conducted via Wiley rather than Ovid as listed. This was raised as a clarification question and the company confirmed that Wiley had been used.

		There was also an error at line 19 in the update searches – this was raised as a clarification question. The company provided the correct line in their response.
Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, and grey literature sources and were searched.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was for the update searches.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive. There were a couple of missed condition terms, e.g. mast-cell disease(s) and mastocytoses. However, this is unlikely to have made much difference to the literature.
Were any search restrictions applied appropriate?	YES	Animal papers and irrelevant paper types were removed appropriately.
Were any search filters used validated and referenced?	UNCLEAR	There were no references for search filters.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 4. EAG APPRAISAL OF COST AND HEALTHCARE RESOURCE EVIDENCE IDENTIFICATION

The original company submission included searches to identify cost and healthcare resource identification, measurement and valuation studies for adult patients with advanced systemic mastocytosis. A description of the searches and all the search strategies were included in Appendix I (pp. 115-131).

In response to the EAG's points for clarification the company provided additional information and corrections to errors identified by the EAG.

Table 37 EAG appraisal of cost and healthcare resource evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	The documentation is mostly clear and comprehensive. In the original company submission, the update searches of the Cochrane library databases appeared to have been conducted via Wiley rather than Ovid as listed. This was raised as a clarification question and the company confirmed that Wiley had been used.

Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, and grey literature sources and were searched.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. The only use of date limits was for the update searches.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive. There were a couple of missed condition terms, e.g. mast-cell disease(s) and mastocytoses. However, this is unlikely to have made much difference to the literature.
Were any search restrictions applied appropriate?	N/A	No search restrictions were applied.
Were any search filters used validated and referenced?	UNCLEAR	There were no references for search filters.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 5. EAG APPRAISAL OF TARGETED LITERATURE REVIEWS

The original company submission included four targeted literature reviews (TLRs) in Appendix P (pp. 1-30). These were as follows:

- TLR to identify QLQ-C30 to EQ-D mapping algorithm;
- TLR to identify health state utility values after AdvSM progression;
- TLR to define the QoL during and after allo-HSCT;
- TLR to define HSCT efficacy in AdvSM patients.

The methodologies and documentation for the four TLRs within Appendix P were unusual, unclear and are not to the professional standard of the other search strategies throughout the submission. The company were asked to clarify why the literature reviews documented in Appendix P were not conducted systematically and whether any relevant evidence was missed as a result. In response, the company explained that the four searches were conducted in the context of informing model parameters and that they had therefore adhered to the advice in NICE DSU Technical support document 13 (TSD13) to restrict the number of sources searched and the search terms.

The following issues were noted with the methodology and reporting of the TLRs:

a) For all TLRs, it was not clear which exact dates the searches were performed so we could not tell how up to date the evidence was. In response, the company noted that there was a 'two-year gap between the execution of the TLRs and the NICE submission date' but exact dates were not provided.

b) For the TLR to identify QLQ-C30 to EQ-5D mapping algorithm, not all the inclusion criteria were searched for. In addition, the Embase strategies did not list the platform used and had no search syntax – if searched on the Ovid platform, search terms would default to the mp (multipurpose) field code, which is not the same as searching all fields as reported.

c) For the TLR to identify QLQ-C30 to EQ-5D mapping algorithm the company document 12 search lines but then appear to have only searched the results of line 11, which was misleading. In response, the company explained that the other lines were included to report 'all the terms that were considered to build the search lines'. However, this is not standard practice in reporting search strategies and the additional data was not useful. The clarification that certain lines 'yielded an excessive number of results' also highlighted that it would have been better to have used a professional information specialist to search the literature and to report the searches and methodology.

d) For the TLR to define the QoL during and after allo-HSCT and the TLR to define HSCT efficacy in AdvSM patients, only MeSH terms and no free-text terms were searched. The company clarified that this was done to minimise irrelevant papers and stated that 'free text search was used to define allo-HSCT in patients with AdvSM'. However, this is not consistent with the documentation which shows that only MeSH terms were used.

e) For the TLR to identify health state utility values after AdvSM, it is not clear which search fields were searched on PubMed. The company explained that the fields listed were searched. However, no search fields were specified. It is possible that the company searched all fields on PubMed but we cannot be certain of this as the number of results for these searches, even if conducted several years ago, should have been higher. The documentation of the searches means it is difficult to fully understand or scrutinise the searches and their methodology.

APPENDIX 6. EAG APPRAISAL OF ALLO-HSCT SCENARIO MODEL

This appendix presents a summary of an additional model structure that was presented as a scenario analysis in Appendix N of the CS, in which allogenic haematopoietic stem cell transplantation (allo-HSCT) is considered as a potential curative treatment option for a very small proportion of patients with AdvSM who achieve complete remission following systemic treatment.

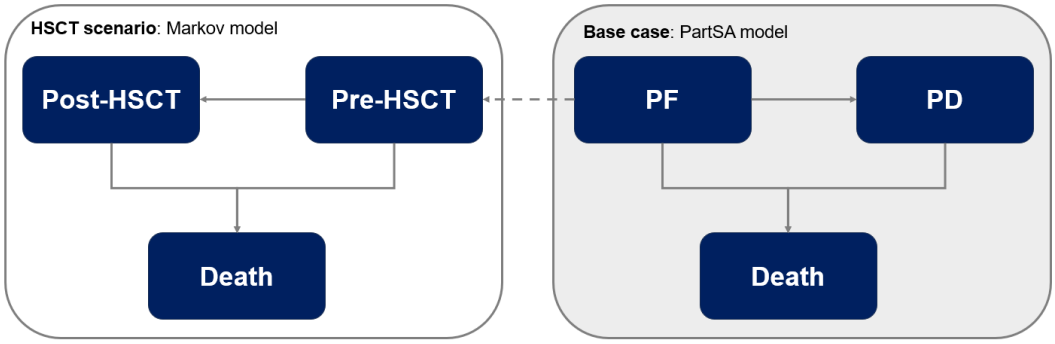
The CS states that "according to clinical expert feedback the rate of increased allo-HSCT eligibility and the data regarding outcomes following treatment with avapritinib and subsequent HSCT are subject to uncertainty". Therefore, allo-HSCT was excluded from the company's base case and the parameter inputs relating to the allo-HSCT model are only presented in Appendix N of the CS.

Below the EAG highlights a number of major concerns with the company's model for the inclusion of allo-HSCT, largely related to the hypothetical nature of several key parameters and the oversimplification of the model. The EAG concludes that the allo-HSCT model is not suitable for decision making.

Summary of company's submission

The potential impact of avapritinib in increasing the proportion of patients capable of undergoing allo-HSCT compared to comparators is explored in a scenario analysis using a separate *de novo* model. This model allows the inclusion of allo-HSCT as a possible treatment option for a proportion of patients who have responded to the treatment. The allo-HSCT model structure is via a parallel health state Markov model, where a proportion of the PF cohort in the base case model may enter the health states associated with allo-HSCT, consisting of pre-allo-HSCT, post-allo-HSCT and death (see Figure 6).

Figure 6 Allo-HSCT scenario model structure (replicated from Figure 27 of the CS)



Abbreviations: Allo-HSCT, allogenic haematopoietic stem cell transplantation; PF, progression-free; PD, progressive disease

All patients eligible for HSCT start in the pre-HSCT state and remain there until a predetermined timepoint when HSCT occurs (i.e., after one year for this scenario analysis). The costs (drug acquisition and disease management), utility, and OS for those in this health state are the same as those in the PF health state, depending on treatment initiated and line of treatment. Disease progression and discontinuation are not allowed in this state and those who enter this Markov model cannot revert back to the PartSA model.

After the waiting time for HSCT, all surviving patients transition to the post-HSCT state. After undergoing HSCT, patients are assumed to experience no further disease progression. The health state utility value is derived from Grulke et al., (2011)[55] mapped from EORTC QLQ-30 to EQ-5D by Young mapping algorithm [39]. The cost of HSCT is a one-off cost of £40,553. Patients post-HSCT do not receive any treatment. The health state cost is incurred for 1 year post-HSCT, at £197, in line with TA523 [56]. Beyond month 12, patients are assumed to be cured, incurring zero costs thereafter. Overall mortality from this health state is derived from Ustun et al., (2014) [57] and is extrapolated using an exponential parametric function, which is assessed as the best fit survival curve. The death risk associated with HSCT is assumed to be absorbed within the overall mortality reported in Ustun et al., (2014)[57].

Avapritinib is modelled to affect QALYs by increasing the proportion of patients eligible for allo-HSCT – the treatment option that is "*considered the only potential curative option for patients with AdvSM*" – compared to comparators. Allo-HSCT is also associated with high utility values: 0.62 in the first month post-HSCT, 0.76 in months 2-6 and 0.796 from month six onwards. There are two primary components that influence the proportion of patients undergoing allo-HSCT which are i) the response rates, dependent on the treatment initiated, and ii) allo-HSCT eligibility, independent of the treatment initiated and consists of the clinical selection process, suitability for HSCT, and donor availability.

Patients with either complete response or overall response (excluding complete response) are considered eligible for HSCT. For avapritinib, the response rates are sourced from PATHFINDER September 2022 cut-off, using IWG-MRT-ECNM criteria and stratified by disease subtypes and lines of treatment. The odds ratios of response rates between midostaurin and avapritinib are estimated using an unanchored MAIC utilising the pooled RAC-RE population of PATHFINDER and EXPLORER, all doses, compared to a pooled effect between studies D2201 and A2213 for midostaurin. The odds ratios for avapritinib vs 1L midostaurin are estimated to be 12.39 (95% CI 1.14 –134.58) for complete response and 3.83 (95% CI 2.25 – 6.532) for overall response (excluding complete response), applied equally for disease subtypes. The response rates for 2L+ BAT and 2L+ cladribine are assumed to be zero.

Among those who have any kind of response to treatment, a clinical selection process resulted in [redacted]% being classified as suitable for HSCT, based on expert advice to the company. Of those selected, only 50% are assumed to be fit for HSCT. Those fit for HSCT would then require a donor. A targeted literature review identified an estimate of 26% of patients having a sibling donor, while for those without a sibling donor, non-related donor availability of 67%, which resulted in an overall donor availability of 76%. When taking account of all three components above, it is estimated that only [redacted]% of responders receive allo-HSCT.

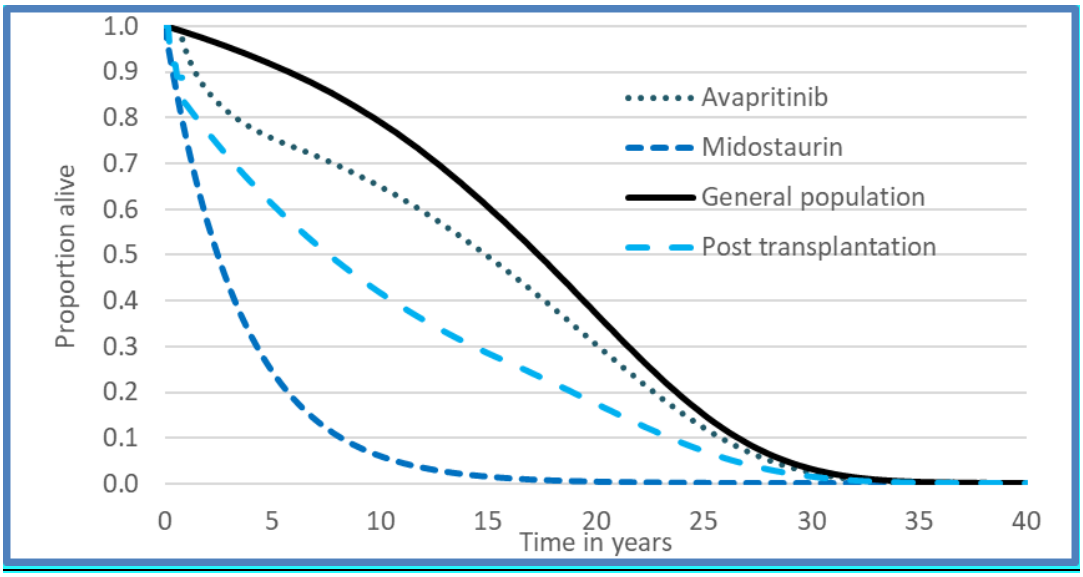
Points for critique

The EAG notes that the clinical advisors to the company suggested that only the right-hand panel in Figure 6 (the base case PartSA model) of this allo-HSCT model is reflective of AdvSM events, and that patients who have progressive disease (or high-risk stable disease) may also be considered for HSCT[58]. Furthermore, since allo-HSCT is suitable for only a very small proportion of patients, the inclusion of this treatment option is unlikely to have a substantial impact on the overall cost-effectiveness of avapritinib. The EAG considers this model structure to be unsuitable for decision making and highlights a number of key concerns relating to the parameterisation of the model:

- The EAG is concerned that the actual number of patients undergoing HSCT is not available in the pivotal trials. Since this treatment effect is unobserved, the company uses response rates as proxies to define eligibility for HSCT. During the clarification stage, the company reported [redacted] patients and [redacted] patients potentially undergoing transplantation in PATHFINDER and EXPLORER respectively. However, it remains unclear whether those patients did undergo transplantation;
- As previously discussed in Section 3.4.3, the EAG considers the MAIC comparing complete response rate between avapritinib and 1L midostaurin to be highly uncertain due to small numbers of patients achieving a complete response as per the IWG-MRT-ECNM criteria (1 in the D2201 trial, 4 in the pooled PATHFINDER and EXPLORER trials). Furthermore, the assumption that no patients in 2L+ cladribine/BAT are eligible for HSCT is note supported by evidence in the CS;
- Since not all responders end up receiving transplantation, the company uses external evidence to define the proportion of responders eligible for transplantation by a sequential selection process, which the EAG considers to be highly uncertain. Key parameters in this selection process appears to be based on weak evidence (i.e., elicited from only two haematologist consultants, whose opinions diverge), or assumptions (i.e., the proportion of patients classified as fit for transplantation post-clinical selection is assumed to be 50%).
- The EAG notes that the clinical advisors to the company provided a cut-off age for transplant of 70 years[58]. The mean starting ages in the model based on the baseline population characteristics of PATHFINDER are near this threshold (68.29 years in the 1L and 66.55 years in the 2L+ population); therefore, the viability of allo-HSCT as a treatment option may be constrained.
- The EAG considers a fixed waiting time for allo-HSCT (1 year) to be highly uncertain;
- The EAG considers the overall survival post-transplantation, which is based on external evidence from Ustun et al., (2014) [57] to be implausible. As seen in Figure 7, the overall survival of those undergoing transplantation, which is considered 'curative' by the company, is lower than that of patients remaining on avapritinib without transplantation. Although this

implausibility is mitigated by the implementation of a duration of treatment benefit of 5 years (as in the base case), the EAG considers that this parameter lacks face validity.

Figure 7 Overall survival in the allo-HSCT model



- Adverse events related to stem cell transplantation are not considered in the model. In the previous appraisal (TA523[56]), where stem cell transplantation was included as a viable treatment option for patients with acute myeloid leukemia, the Appraisal Committee stated that *"graft versus host disease, a potential adverse effect of stem cell transplant, could have a significant impact on quality of life*" and thus should be considered in the model;
- The assumption of no disease progression during the waiting period and post-transplantation appears to be highly uncertain and lacks supporting evidence;
- The assumption of zero cost associated with monitoring patients undergoing transplantation beyond 12 months is deemed implausible, a critique point highlighted previously in TA523 by the Appraisal Committee.[56]

In addition, the EAG identified an error in the model in relation to the waiting time which the CS stated should be set at 1 year for this scenario analysis but it was set at 2 years in the electronic version of the model.

In summary, due to the major concerns with the company's model for the inclusion of allo-HSCT, the EAG concludes that the allo-HSCT model is not suitable for decision making and this scenario analysis should not be considered further.

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 7 May 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Lack of clarity of what constitutes "best available therapy" at second or subsequent lines

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65, paragraph 3, lines 4-5 – misleading comparator	Please replace: "(ii) *avapritinib* compared with cladribine, or best available therapy (BAT)" With the following: "(ii) *avapritinib* compared with cladribine, or best available therapy (BAT), as proxy for cladribine." Please refer to "BAT" analysis as "BAT, as a proxy for cladribine" in the report moving forward.	The comparators included in the economic analysis consist of midostaurin in 1L and cladribine in 2L+ settings, see Company Submission (CS) Table 29. The analysis involving cladribine has small patient numbers (n=27) and high levels of uncertainty (overall survival HR: [redacted] non-significant). Therefore, the comparison involving BAT is used for illustration purposes only and is as a proxy for cladribine.	EAG report amended accordingly.
Page 71, paragraph 3, lines 7-9 – misinterpretation of BAT (as a proxy for cladribine) analysis	Please replace: "this is reflected in the company's separate comparison with BAT in the 2L+ population setting, where BAT consists of a mixture of therapies,	Although Blueprint Medicines provided analysis versus BAT (as a proxy for cladribine), this was for illustration purposes, see explanation above and as a result in the company's base case, distribution of therapies	This is not a factual inaccuracy. The OS for 2L+ BAT (as a proxy for cladribine) is based on a mixture of therapies, including [redacted] of patients who received midostaurin. The

	including [redacted] of patients receiving midostaurin." With the following: "this is reflected in the company's separate comparison with BAT (as a proxy for cladribine) in the 2L+ population setting, where BAT consists of a mixture of therapies, including [redacted] of patients receiving midostaurin. However, as BAT is used as an exploratory analysis for cladribine, the distribution of therapies such as midostaurin, interferons, imatinib and AML like medicines are set to 0% for cost calculation purposes, reflecting cladribine as the sole comparator in the company's base case."	such as midostaurin, interferons, imatinib and AML like medicines are set to 0%.	sentence on page 71 is referring to the fact that some patients receive midostaurin in the 2L+ population as demonstrated in the comparison with 2L+ BAT where outcomes are based on a proportion of patients who received midostaurin at 2L+.
Page 72, paragraph 4, lines 5-7 – misleading BAT (as a proxy for cladribine) analysis.	Please replace: "the company have compared avapritinib with cladribine and a separate comparison with BAT, which consists of a mixture of therapies, including midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-	Despite distributions of other therapies being set to 0% for cost calculation purposes, reflecting cladribine as the sole comparator, the clinical efficacy has kept the outcome of the mix of BAT. This is therefore considered a conservative scenario, by	Sentence amended to make it clear that in the comparison with 2L+ BAT as a proxy for cladribine, clinical efficacy (including OS) stems from a mixture of therapies, including midostaurin ([redacted]%),

	interferon alpha ([redacted]%), and hydroxyurea ([redacted]%)." With the following: "the company have compared avapritinib with cladribine and a separate comparison with BAT (as a proxy for cladribine), whereby clinical efficacy stems from a mixture of therapies, including midostaurin ([redacted]%), cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%). Consequently, clinical efficacy of cladribine is likely to be overestimated,[1] given that midostaurin constitutes [redacted] of the BAT basket"	increasing the efficacy of cladribine, consequently reducing the actual incremental efficacy of avapritinib.	cladribine ([redacted]%), interferon alpha/peg-interferon alpha ([redacted]%), and hydroxyurea ([redacted]%). This paragraph and section of the report is referring to what the intervention and comparators are, and the relevance of these to the decision problem. It is not referring to the treatment effectiveness of the intervention and comparators, which is discussed in Section 4.2.6.

Issue 2 Separation of the population by treatment line

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Table Issue 2, column 2, paragraph 1, line 2-5.	Please consider removing: "which implies that a separate recommendation for avapritinib is required in those who have received	Blueprint Medicines have provided analyses assessing the whole anticipated licenced indication, which is anticipated to be as a	Issue 2 amended accordingly. However, the EAG is making the point that the company have not presented a

	prior systemic therapies (2L+ population) from those who have not (1L population), whereas the NICE recommendation for midostaurin is not restricted to the 1L population."	[redacted], to be considered by committee. The recommendation required is to be determined by the committee.	cost-effectiveness comparison of avapritinib with midostaurin (or any other comparator) in the overall population, i.e., not separated by line of treatment.
Page 67, paragraph 1, lines 3-7 – uncertainty regarding MHRA license indication.	Please remove "uncertainty about" and "while the EU marketing authorisation in March 2022 is restricted to the treatment of adult patients after at least one systemic therapy", in the following statement: "This difference is partly a consequence of the availability of midostaurin since TA728, but it may also be linked to ~~uncertainty about~~ the anticipated Medicines and Healthcare products Regulatory Agency (MHRA) licensed indication for avapritinib, where the company is seeking GB marketing authorisation for the treatment of [redacted]	Feedback from MHRA suggests there were no major objections to the anticipated licenced indication, that is as a [redacted]	Sentence amended to remove "uncertainty about". The EAG have not removed the part of the sentence which states "the EU marketing authorisation in March 2022 is restricted to the treatment of adult patients after at least one systemic therapy", because this is not factually inaccurate. The company submission states this on page 18 under marketing

	[redacted] ~~while the EU marketing authorisation in March 2022 is restricted to the treatment of adult patients after at least one systemic therapy~~."		authorisation/CE mark status.
Page 71, paragraph 3, lines 1-4 -	Please remove "and implies that a separate recommendation for avapritinib is required in those who have received prior systemic therapies from those who have not." from the following statement: "The EAG's primary concern in relation to the population used in the model is the separation of the population by line of treatment, which is not sufficiently justified in the CS. ~~and implies that a separate recommendation for avapritinib is required in those who have received prior systemic therapies from those who have not~~."	Blueprint Medicines have provided analyses assessing the whole anticipated licenced indication, which is anticipated to be as a [redacted], to be considered by committee. The recommendation required is to be determined by the committee.	Sentence amended to remove any judgement on recommendation required. The sentence is amended to, "The EAG's primary concern in relation to the population used in the model is the separation of the population by line of treatment, which is not sufficiently justified in the CS and a separate cost-effectiveness analysis of avapritinib is presented for those who have received prior systemic therapies from those who have not."

Issue 3 Limitations of the effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Table Issue 3, column 2, row 2, lines 1–2 – EXPLORER incorrectly described as ongoing.	Please replace: "The effectiveness evidence comes from two ongoing single arm studies for which results are immature." With the following: "The effectiveness evidence comes from two single arm studies, of which one is completed and one is still ongoing and results are immature."	The phase 1 EXPLORER study was incorrectly described as ongoing in the EAG report. EXPLORER has been completed with the final read-out being from April 2023.	Amended

Issue 4 Limitations of the indirect treatment comparisons

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 33, section 3.1.5, paragraph 1, lines 6–8 – clarification on pooling of studies	Please replace: In some of the indirect treatment comparison analyses, the PATHFINDER and EXPLORER studies from the May/June 2020 data cut-off, and April 2021 data cut-off were pooled together.	The statement in the EAG report could be interpreted as the 2020 and 2021 data cut-offs were pooled *together*, however they were not.	Accept company's request but amend wording proposed to: "In the indirect treatment comparison analyses, results from the PATHFINDER and

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	With the following: In the indirect treatment comparison analyses, results from the PATHFINDER and EXPLORER studies were pooled together. For the MAIC as reported in Pilkington et al. (2022) the May/June 2020 data cut-offs were pooled, while for the most recent MAIC ITC report the April 2021 data cut-offs were pooled.		EXPLORER studies were pooled together. For the MAIC as reported in Pilkington et al. (2022), and initially provided in the company submission, the May/June 2020 data cut-offs were pooled, while in the most recent MAIC ITC report, provided at the clarification stage, the April 2021 data cut-offs were pooled."
Page 55, Table 12, Column 1, Row 11 – typographical error	Please replace: Leukocyte count ≥16 × 109/L, (n [%]) With the following (exponent written as superscript): Leukocyte count ≥16 × 10^9/L, (n [%])	Typographical error.	Amended
Page 59, paragraph 1 – misleading statement suggests company lacked	Please replace: "The EAG were presented with few details of the methods and results from the IPTW, meaning it has been difficult	Blueprint medicines provided the EAG with the full clinical study report (CSR) and protocol of the external control study (ECS), which	Not a factual inaccuracy. The company's answer to clarification questions requiring additional details on the IPTW

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
transparency in presenting the IPTW	to determine whether the analyses were appropriately conducted. The company provided limited information on the doubly robust estimation methods used to adjust baseline characteristics between the avapritinib studies and the ECS and therefore it is difficult to determine how well the populations have been matched following adjustment, and the extent to which particular participant characteristics are over/under-represented based on the distribution of weights in the analysis." With the following: "The company provided the ECS protocol which outlined the methods used to conduct the IPTW, as well as a thorough summary of results for the outcomes of OS and DoT. In response to clarification questions, the company provided baseline characteristics before and after IPTW-weighting in the subgroups for overall survival."	included pooled data from PATHFINDER 2021 and EXPLORER 2021 to inform avapritinib estimates. In addition, a full set of overall survival (OS) and duration of treatment (DoT) results were provided for the IPTW using the PATHFINDER 2022 data cut to inform avapritinib estimates. In addition, in response to the clarification questions, the company provided the EAG with baseline characteristics before and after IPTW-weighting in the subgroups for overall survival.	methodology were answered by stating details would be provided at a later date (details were not provided by the date of writing this report). The EAG has amended for additional clarity. "The EAG were presented with insufficient details of the methods and results from the **population adjustment methods** used in the IPTW, meaning it has been difficult to determine whether the analyses were appropriately conducted. **The company stated that the details requested in clarification question A20, would be provided at a 'later**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			date', but these were not received at the time of writing this report. It is therefore difficult to determine how well the populations have been matched following adjustment, and the extent to which particular participant characteristics are over/under-represented based on the distribution of weights in the analysis."
Page 62, paragraph 8 – misleading statement suggests company lacked transparency in presenting the IPTW	Please replace: 'In the absence of detailed methodology and results for the IPTW, the MAIC provides additional evidence on the clinical effectiveness of avapritinib compared to midostaurin.' With the following:	Blueprint medicines provided the EAG with the full CSR and protocol of the ECS, which included pooled data from PATHFINDER 2021 and EXPLORER 2021 to inform avapritinib estimates. In addition, a full set of OS and DoT results were provided for the IPTW using the	Not a factual inaccuracy. The company's answer to clarification questions requiring additional details on the IPTW methodology were answered by stating details would be provided at a 'later date' (details were not

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	'The MAIC provides additional evidence on the clinical effectiveness of avapritinib compared to midostaurin.'	PATHFINDER 2022 data cut-off to inform avapritinib estimates. Please clarify the aspects of the methodology and results that were unclear.	provided by the date of writing this report). The EAG has amended for additional clarity. 'In the absence of detailed methodology and results for the **population adjustments** in the IPTW, the MAIC provides additional evidence on the clinical effectiveness of avapritinib compared to midostaurin.'

Issue 5 Lack of consistency in the source of evidence used to inform the different survival parameters in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Table Issue 5, Row 2, Line 4-5 – wording implies company were able	Please replace: "The company uses the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW for the comparisons	It is not possible to do an IPTW or adjusted analysis for the comparators in the ECS because disease progression	Sentence amended as suggested for additional clarity.

to conduct an IPTW adjusted analysis for PFS	with the relevant comparators in the 1L and 2L+ populations, but uses the RAC-RE population unweighted analysis for PFS for avapritinib." With the following: "The company uses the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW for the comparisons with the relevant comparators in the 1L and 2L+ populations and uses the RAC-RE population unweighted analysis for PFS for avapritinib due to the absence of PFS data collected in ECS and safety population."	was either not recorded or was documented inconsistently with the evaluative mIWG- MRT-ECN criteria used in PATHFINDER.	

Issue 6 Immaturity of the OS data used in the extrapolations

Description of problem	Description of proposed amendment	Justification for amendment
None identified	-	-

Issue 7 Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS

Description of problem	Description of proposed amendment	Justification for amendment
None identified	-	-

Issue 8 Source of evidence used to inform time on treatment in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86, paragraph 1, lines 9-10 – IPTW ITC for TOT was explored as a scenario in company submission	Please replace: "(v) an IPTW ITC of avapritinib and the comparators is not used for the TOT curves in the model." With the following: "(v) an IPTW ITC of avapritinib and the comparators is not used for the TOT curves in the company's base case."	IPTW adjusted analysis was included in the model and explored as a scenario analysis.	No amendment necessary. The EAG sentence states "The EAG considers the choice of TOT curve for avapritinib as a major limitation of the company's base case analysis because:…(v) an IPTW ITC of avapritinib and the comparators is not used for the TOT curves in the model.", i.e. the EAG sentence already makes it clear that the limitations are

<table>
<tr><td></td><td></td><td></td><td>referring to the company’s base case analysis.</td></tr>
<tr><td>Page 86-87, table 16 – incorrect reporting of median duration of treatment</td><td>Please replace:
<table><tr><th>TOT curve</th><th>Comparison</th><th>1L vs. midostaurin</th><th>2L+ vs. cladribine</th><th>2L+ vs. BAT</th></tr><tr><td rowspan="3">Company base case: CUP for avapritinib and unweighted ECS for comparator</td><td>Avapritinib</td><td>16.4</td><td>16.4</td><td>16.4</td></tr><tr><td>Comparator</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Difference:</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td rowspan="3">EAG preferred base case: IPTW from PATHFINDER and ECS for avapritinib and comparators*</td><td>Avapritinib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Comparator</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Difference:</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>
With the following:</td><td>CUP median time on treatment was reported as 505 days, equating to 16.56 months and unweighted/weighted ECS median time on treatment for comparators were incorrectly reported, correct results can be found in the company’s model.</td><td>No amendment necessary. The median TOT reported in Table 16 is based on the median time from the parametric curves that are used in the base case analyses, i.e., parametric curves are used in the company’s analyses to extrapolate reported median TOT over time and it is the median of these curves that are reported in Table 16.

For increased clarity, the EAG has amended the caption of Table 16 to indicate that the values reflect the median from the parametric TOT curves used in the base case analyses.</td></tr>
</table>

TOT curve	Comparison	1L vs. midostaurin	2L+ vs. cladribine	2L+ vs. BAT
Company base case: CUP for avapritinib and unweighted ECS for comparator	Avapritinib	16.6	16.6	16.6
	Comparator	[redacted]	[redacted]	[redacted]
	Difference:	[redacted]	[redacted]	[redacted]
EAG preferred base case: IPTW from PATHFINDER and ECS for avapritinib and comparators*	Avapritinib	[redacted]	[redacted]	[redacted]
	Comparator	[redacted]	[redacted]	[redacted]
	Difference:	[redacted]	[redacted]	[redacted]

Issue 9 Uncertain duration of treatment benefit for avapritinib

Description of problem	Description of proposed amendment	Justification for amendment
None identified	-	-

Issue 10 Exclusion of subsequent therapy costs

Description of problem	Description of proposed amendment	Justification for amendment
None identified	-	-

Issue 11 Uncertainty in the progression-free and progressive disease health state utility values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93, paragraph 2 – time dependent utility analysis	Please remove: "The EAG notes that no consideration was given to the derivation of time-dependent utility values from the available health related quality of life (HRQoL) observations up to week 64, where the mapped PF utility could be derived as a function of time and extrapolated over the long-term to allow for any potential changes in quality of life as a function of time since start of treatment."	Blueprint Medicines considered time dependent utilities, however due to small sample sizes (n=[redacted], at week 64, PATHFINDER, September 2022 data cut-off, 1L) this was not viable and subject to uncertainty.	Amended to add "in the company submission". The company submission (or company response to EAG points for clarification document) does not indicate that the company considered time-dependent utility values. The justification provided here is new information to the EAG, provided after the EAR was written.

(please cut and paste further tables as necessary)

Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 23 and 112	Dominant ICERs not marked confidential	Throughout the document dominant ICERs are not marked confidential. Please can EAG mark all ICERs confidential throughout the document. Specifically, in: **Table 2, rows 2-3, column 4** **Table 24, rows 2-38, column 8**	Apologies for this error in the marking. Now amended throughout.
Page 26	QALYs marked confidential	To remove underline in **table 26, column 5.**	Amended.
Page 96, paragraph 4, line 1	Data on file, anti-sickness medication unmarked – based on clinical insights	To read: "The CS includes a once daily anti-sickness tablet, 8mg ondansetron, for [redacted] of those receiving midostaurin, with a list price of £3.47 per pack of 100 tablets."	Amended.

General

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the document: date of providing additional analyses on most recent PATHFINDER data cut-off (September 2023) provided. Namely the following locations: - p11, paragraph 2, lines 2–5 - Page 15, Table Issue 3, column 2, row 2, lines 8–10 - Page 35, paragraph 3 - Page 40, paragraph 4, lines 4–6 - Page 41, Section 3.2.1.5, paragraph 3, lines 3–4 - Page 42, paragraph 3, lines 1–3 - Page 45, section 3.2.2.5, lines 6-7 - Page 55, paragraph 2, lines 4–5	Please replace any statements such as: *"A more recent data cut-off is available but updated analyses were not provided to the EAG."* Or *"The company stated in their response that this information would be provided with the updated data cut-off (September 2023) at a 'later date', but at the date of submitting this report, no details have yet been provided to the EAG."* With wording that clarifies that the new data will be provided to the EAG on 5 July 2024. Examples could include the following wording: "*A more recent data cut-off is available but updated analyses were not provided to the EAG. The company will*	The September 2023 data cut-off from PATHFINDER was not yet available to be incorporated into the submission or clarification response. Blueprint Medicines can now confirm that the additional analyses with the most recent data cut-off will be made available to the EAG on 5 July 2024.	This is not a factual inaccuracy. The company's proposed date was not known to the EAG at the time of writing. The company's response to EAG clarifications stated at a "later date", i.e., a date was not provided to the EAG at the time.

- Page 56 (last line)–57 (first line) - Page 58, section 4.3.2.3, lines 4–6 - Page 64, lines 5–10 - Page 80, paragraph 2, lines 19-20 - Page 93, paragraph 1, line 8-9	*provide updated analyses to The EAG on 5 July 2024."* *Or* "*In response to the EAG's clarification questions, the company stated that an additional data cut-off was available (September 2023). This was not available to submit as part of the clarification response, it will be provided to the EAG on 5 July 2024."*		
Page 25, paragraph 2, lines 5–6 – clarifying that the company has applied for MA in the UK	Please replace: Avapritinib does not currently have a marketing authorisation in the United Kingdom (UK) for treating AdvSM. With the following: Avapritinib has an anticipated indication of monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL). An application to the MHRA was made on [redacted] and the	Currently this statement has incomplete information on the regulatory status of avapritinib.	Not a factual inaccuracy. The anticipated date of GB marketing authorisation was not known at the time of submission of the report and the license has not yet been granted.

	anticipated date of GB marketing authorisation is [redacted].		
Page 35, paragraph 1, line 3 – typographical error in the number of days after final treatment when end of treatment visit takes place	Please replace “after 7021 days” With “after 7–21 days”	Typographical error mistakenly suggests the end of treatment visit in PATHFINDER takes place 7021 days after last dose of treatment, whereas this is in fact 14 (±7) days as per the PATHFINDER CSR.	Amended
Page 67, paragraph 1, line 6 – GB marketing authorisation	Please replace: “treatment of [redacted]” With the following: “treatment of [redacted]	To align wording with exact anticipated GB marketing authorisation.	Amended
Page 70, paragraph 4, lines 1-2 – Great Britain marketing authorisation	Please replace: “The population considered in the model is adult patients with AdvSM[redacted] With the following:	As above.	Amended

	The population considered in the model is adult patients with AdvSM, [redacted]		
Page 74, paragraph 4, line 8 – incorrectly reported patient numbers	Please replace: "In the safety population of PATHFINDER for 2L+, a very high percentage of patients (83.6%) received midostaurin as prior systemic therapy, which means that less than 20% of the 2L+ cohort from PATHFINDER (corresponding to 13 patients) is available to consider outcomes in patients who did not receive prior midostaurin." With the following: "In the safety population of PATHFINDER for 2L+, a very high percentage of patients (83.6%) received midostaurin as prior systemic therapy, which means that less than 20% of the 2L+ cohort from PATHFINDER (corresponding to 11	Table 8 in CS reports 56 out of 67 patients in PATHFINDER 2L+ setting receive prior midostaurin. Resulting in 11 patients who did not receive prior midostaurin.	Amended.

	patients) is available to consider outcomes in patients who did not receive prior midostaurin.”		
Page 74, paragraph 4, line 9 - aligning wording with data reported	Please replace: “Therefore, the limited number of patients in PATHFINDER who were treatment naïve (n=38).” With the following: “Therefore, the limited number of patients in PATHFINDER safety population who were treatment naïve (n=38).”	For full transparency and to distinguish from full PATHFINDER population.	Amended.
Page 94, table 19, row 4, column 2 – incorrect reporting of midostaurin costs	Please replace: £24,393 per cycle (monthly) With the following: £24,398 per cycle (monthly)	Incorrect reporting of monthly cycle cost of midostaurin, as per company’s model.	Amended.

References

1. Lübke J, Schwaab J, Naumann N et al. Superior efficacy of midostaurin over cladribine in advanced systemic mastocytosis: a registry-based analysis. *Journal of Clinical Oncology* 2022, 40, 1783-1794.

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **14 June 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 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)	Blueprint Medicines
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines	Yes	Blueprint Medicines agrees with the EAG that midostaurin is the most relevant comparator for the first-line (1L) treatment of advanced systemic mastocytosis (AdvSM).[1] In addition, the EAG's concerns regarding best available therapy (BAT) as a comparator at second or subsequent lines (2L+) of therapy have been addressed by removing this comparator from the updated base case.[1] In the small proportion of patients who continue treatment in the 2L+ setting, options are limited, and the most appropriate comparator is cladribine. This is supported by clinical expert opinion from two consultant haematologists in England that cladribine is the only interim solution to reduce disease bulk and the predominant treatment of choice after tyrosine kinase inhibitors (TKIs), particularly in patients with high disease bulk.[2] In the company's original base case, a comparison of 2L+ avapritinib and 2L+ cladribine was not feasible as overall survival (OS) outcomes from the external control study (ECS), adjusted using inverse probability of treatment weighting (IPTW), had not yet reached statistical significance when using PATHFINDER 2022 data for the avapritinib cohort. In the updated ECS using the recently available data from pooled PATHFINDER 2023 and EXPLORER 2023 for the avapritinib cohort, the adjusted OS comparison reached statistical significance

		(hazard ratio [HR]: [redacted]; 95% confidence interval [CI]: [redacted], [redacted]; [redacted]) and was used in the model to inform a comparison between 2L+ avapritinib and 2L+ cladribine.[3] In summary, the following comparisons are the most relevant to clinical practice, as agreed with clinical experts, and have been included in the company's revised base case: • 1L avapritinib versus 1L midostaurin • 2L+ avapritinib versus 2L+ cladribine See Section 3 of the additional evidence addendum provided alongside this response form for full details of the company's revised base case.
Issue 2: Separation of the population by treatment line	No	The EAG advised that a comparison should be carried out for avapritinib compared with midostaurin across all lines of therapy (i.e. in an 'all lines' population), which would include a mix of patients that have not received prior therapy (1L) and those that have received prior therapy (2L+).[1] However, the company has not presented this requested analysis as it is not reflective of clinical practice in England, where midostaurin is well-defined in the treatment pathway as a 1L option. Midostaurin is the only licensed treatment option for patients with AdvSM in the UK, including all three subtypes (aggressive systemic mastocytosis [ASM], systemic mastocytosis with an associated haematologic neoplasm [SM-AHN] and mast cell leukaemia [MCL]), and is the only treatment recommended by NICE in this indication.[4] Therefore, it is expected that all patients with AdvSM would be initiated on treatment with midostaurin at 1L, which has been confirmed by feedback from two consultant haematologists in England.[2]
Issue 3: Limitations of the effectiveness evidence	Yes	To address uncertainty in the clinical evidence due to data immaturity, Blueprint Medicines has provided an additional evidence addendum alongside this response form with longer-term (≥3 years) evidence supporting the clinical value of avapritinib. This addendum includes updated data from:[3,5,6] • PATHFINDER (15 September 2023 data cut-off, 200 mg starting dose) • PATHFINDER/EXPLORER (15 September 2023 data cut-off for PATHFINDER and 19 January 2023 data cut-off for EXPLORER, 200 mg starting dose) • ECS (using the updated pooled PATHFINDER/EXPLORER data)

		Results from the analyses of PATHFINDER alone and pooled PATHFINDER and EXPLORER, provide longer-term evidence on the safety and efficacy of avapritinib in the largest possible sample size. The updated ECS leverages the latest pooled data and provides further evidence on the comparative efficacy of first-line (1L) treatment with avapritinib to 1L midostaurin, and second-line and beyond (2L+) avapritinib with 2L+ cladribine. The updated pooled PATHFINDER and EXPLORER analysis reflects the longest-term data available in the largest relevant population size for the avapritinib cohort. As acknowledged by the EAG, the baseline characteristics of EXPLORER and PATHFINDER are broadly similar between patients, as anticipated due to the similar eligibility criteria used in both studies, and are reflective of the AdvSM population within the NHS.[1] Therefore, as anticipated, the baseline characteristics from patients in PATHFINDER alone and pooled PATHFINDER and EXPLORER are also similar, demonstrating the appropriateness of pooling data across both studies to allow for the largest relevant population size with the longest-term available data. Results from these updated analyses are provided in Section 2 of the additional evidence addendum (provided alongside this response form) and are summarised below. **PATHFINDER and EXPLORER** The most recent data cut-off for PATHFINDER provides a median of 38 months follow-up, which is an additional 12 months of follow-up data for patients in PATHFINDER compared with the previous data cut-off (September 2022).[5,7] For the pooled analysis, the median follow-up as of the latest data cut-off was 36 months, providing an additional 18 months of follow-up data compared with the previous pooled analysis (April 2021).[3,8] In the latest data cut-off for the PATHFINDER clinical trial, avapritinib maintained its substantial efficacy in patients with AdvSM who initiated avapritinib at a dose of 200 mg. Specifically, an objective response rate (ORR) of [redacted]% (95% CI: [redacted], [redacted]) was observed, consistent with observations from the previous 2022 data cut-off.[5,7] Additionally,

		a complete remission (CR) rate of [redacted]% and complete remission with partial haematologic recovery (CRh) rate of [redacted]% were observed.[5] Similar response rates were observed in the pooled PATHFINDER and EXPLORER analysis (ORR, [redacted]% [95% CI: [redacted], [redacted]]; CR rate, [redacted]%, CRh rate, [redacted]%) compared with PATHFINDER alone.[5] In the September 2023 data-cut off, progression-free survival (PFS) data reached its median in response-evaluable patients treated with avapritinib at a starting dose of 200 mg, with a median PFS of [redacted] months, consistent with pooled EXPLORER and PATHFINDER PFS results (also [redacted] months).[3,7] Overall survival (OS) data from the latest PATHFINDER data cut-off were not mature. [3,7] In the pooled analysis of PATHFINDER and EXPLORER, although median OS was [redacted] for the overall safety population or the 1L subgroup, in 2L+ patients treated with a starting dose of 200 mg avapritinib, a median OS of [redacted] months was observed.[3] As of the latest data cut-offs, substantial reductions in objective disease burden measures, including bone marrow mast cell percentage, serum tryptase levels, *KIT D816V* variant allele fraction (VAF), and spleen volume, were evident in patients in PATHFINDER and in PATHFINDER and EXPLORER (pooled) who initiated avapritinib at a dose of 200 mg.[3,5] In both the PATHFINDER study alone and the pooled analysis with PATHFINDER and EXPLORER, treatment with avapritinib was associated with a clinically meaningful increase in health-related quality of life (HRQoL), with a mean increase in European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire (EORTC-QLQ-C30) global health status score of [redacted] points (standard deviation [SD]: [redacted]) from baseline to cycle 17 of treatment.[3,5] As of the latest data cut-offs, median duration of treatment (DoT) with avapritinib at a starting dose of 200 mg was [redacted] months in PATHFINDER alone and [redacted] months in the pooled PATHFINDER and EXPLORER analysis.[9] The safety profile of avapritinib in patients who initiated treatment at a dose of 200 mg was consistent with the PATHFINDER 2022 data cut-off, with no new safety issues reported.

		External control study In the updated ECS, after adjusting for variables with inverse probability of treatment weighting (IPTW)-weighted Cox proportional hazards models, avapritinib was associated with a significantly improved OS compared to standard of care treatment for AdvSM:[6] • 1L avapritinib vs. 1L midostaurin: o Median OS: [redacted] vs. [redacted] months o Hazard ratio (HR): [redacted]; 95% confidence interval (CI): [redacted], [redacted]; [redacted] • 2L+ avapritinib vs. 2L+ cladribine: o [redacted] months vs. [redacted] months o HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted] Additionally, the updated ECS IPTW showed that avapritinib was associated with a significantly longer DoT compared to 1L midostaurin and 2L+ cladribine, both before and after weighting.[6] • 1L avapritinib vs. 1L midostaurin: o Unweighted: ▪ Avapritinib median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ Midostaurin median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted] o Weighted: ▪ Avapritinib median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ Midostaurin median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted] • 2L+ avapritinib vs. 2L+ cladribine: o Unweighted: ▪ Avapritinib median DoT: [redacted] months (95% CI: [redacted], [redacted])

		▪ Cladribine median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted] ○ Weighted: ▪ Avapritinib median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ Cladribine median DoT: [redacted] months (95% CI: [redacted], [redacted]) ▪ HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted] **Conclusion** Taken together, results from the updated PATHFINDER/EXPLORER and ECS analyses show that avapritinib maintained its substantial efficacy in patients with AdvSM who initiated avapritinib at a dose of 200 mg, as shown by its response to treatment, survival rates, duration of treatment, objective measures of disease burden and health-related quality of life (HRQoL) measures with no new safety issues. The CR rates of avapritinib are of specific note since, considering the lack of CR observed in midostaurin studies,[10] this rate of CR/CRh is unprecedented and provides the opportunity for further curative treatment with allogeneic haematopoietic stem cell transplantation (allo-HSCT).
Issue 4: Limitations of the indirect treatment comparisons	Yes	Blueprint Medicines agrees with the EAG that the ECS IPTW analyses provides the best available comparative clinical evidence to inform the base case for avapritinib versus standard of care (1L midostaurin and 2L+ cladribine).[1] An updated ECS has been provided alongside this response form in the additional evidence addendum, with data for the avapritinib cohort derived from a pooled population of patients receiving an initial dose of 200 mg from the latest data cut-offs for PATHFINDER and EXPLORER (2023).[3,6] Data from EXPLORER and PATHFINDER were pooled to ensure that the longest-term data available, in the largest relevant population size for the avapritinib cohort were reflected in the ECS. OS and duration of treatment (DoT as a proxy for PFS) outcomes from this updated ECS were used to inform the revised base case (see response to Issue 5). Detailed methods of the ECS IPTW were provided previously in the initial company submission. In brief, comparative analyses, adjusting for key baseline covariates, employed a two-step process to obtain an effect estimate that was doubly robust against confounding:

1. Prior to reviewing or analysing outcome data, stabilised IPTW weights were created and applied to balance the differences in key covariates between the 1L avapritinib and 1L midostaurin cohorts, and the 2L+ avapritinib and 2L+ cladribine cohorts.
2. Outcomes were compared between the avapritinib and midostaurin/cladribine cohorts using an IPTW-weighted multivariable Cox proportional hazards model, with further adjustment for remaining imbalances in the distribution of key covariates in the weighted cohorts (i.e., covariates with standardised differences >10%).

As described in the response to Clarification Question A17, the key covariates that were included in the population adjustment in the IPTW were selected a priori during the protocol and statistical analysis plan preparation stage, and were based on the following considerations:

- Covariates that were available in the avapritinib trials (required since otherwise confounding control methods could not be implemented)
- Clinical importance of key prognostic factors or confounders based on published literature and expert opinion, including components of Mutation-Adjusted Risk Score (MARS)[11] and international prognostic scoring system for mastocytosis (IPSM)[12]

Table 1 provides an overview of the key covariates included in the IPTW and the rationale for their inclusion.

Table 1. Overview of the key covariates included in the IPTW and rationale for inclusion

Covariate included in IPTW	Rationale
Age	Age >60 years is a component of the MARS prognostic score. Age ≥60 years is a component of IPSM prognostic score. Age was included as a continuous variable in BLU-285-2405 to allow for finer adjustment.
Sex	Expert opinion and published literature. Kluin-Nelemans et al.[13] identified sex as a strong independent prognostic factor

			in systemic mastocytosis. Authors reported that among patients with ASM or SM-AHN, male patients had significantly inferior OS compared to female patients.
		Region (North America or Europe)	Expert opinion. There can be differences in treatment availability and healthcare practice that are related to patient's outcome across study sites. Yet, no patient from the avapritinib cohort was from the UK site, one of the sites contributing data for the best available therapy cohort. Adjusting for study sites would result in violation of the positivity assumption. Accordingly, region (US vs. Europe) was included as a covariate.
		Performance status as assessed by the ECOG score	Expert opinion. Adjusting for ECOG performance status in cancer studies is important because it helps to account for differences in patients' functional abilities and overall health status, which can significantly impact treatment outcomes, disease progression, and overall survival.
		Anaemia (haemoglobin <10 g/dL)	Anaemia as defined by haemoglobin <10 g/dL is a component of the Mutation-Adjusted Risk Score (MARS) prognostic score.
		Thrombocytopenia (platelets <100 ´ 10^9/L)	Thrombocytopenia as defined by platelets <100 × 10^9/L is a component of the MARS prognostic score.
		AdvSM subtype (SM-AHN, ASM, or MCL)	Expert opinion and published literature. Studies have reported a median OS of ~3.5 years for ASM, 2 years for SM-AHN, and 0.5–2 years for MCL [10,14-16]
		Presence of skin involvement (including reported mastocytosis in the skin or urticaria)	Skin involvement is a component of the IPSM prognostic score.
		Leukocyte count ≥16 × 10^9/L	This is a component of the IPSM prognostic score.
		Serum tryptase ≥125 ng/mL	This is a component of the IPSM prognostic score.
		Testing and number of mutations within the SRSF2/ASXL1/RUNX1 (S/A/R) panel	Presence of one or two or more high molecular risk gene mutations (i.e., S/A/R) is a component of the MARS prognostic score.

		Number of prior LOTs received: Expert opinion. Existing literature suggested that exposure to prior therapy was associated with shortened OS.[10] Types of prior therapy (TKI therapy, cytotoxic therapy, or biologic or other systemic therapy) received: Expert opinion. Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPSM, international prognostic scoring system for mastocytosis; MARS, Mutation-Adjusted Risk Score; MCL, mast cell leukaemia; OS, overall survival; S/A/R, *SRSF2*/*ASXL1*/*RUNX1* gene panel; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; TKI, tyrosine kinase inhibitor. The EAG indicated in their report[1] that their clinical advisers considered *KIT D816V* mutation status, bone marrow mast cell burden and presence of C-findings to be key prognostic variables in AdvSM, which were not adjusted for in the IPTW. As described previously during responses to clarification questions, bone marrow mast cell burden and C-findings may not have been collected in routine practice, and therefore were not available for use within the ECS, which the EAG accepted.[1] These clinical parameters have not been systematically recorded in clinical practice, especially in the earlier times, where clinical experience with the disease was more limited. Including these parameters of pathological response would likely reduce the quality of the data when calculating comparisons against trial data. Additionally, the company explained during clarification questions that the *KITD816V* mutation status was not adjusted for because almost all (>90%) patients in both avapritinib and real-world control cohorts had a KIT mutation, thus the association between *KITD816V* mutation status and treatment was weak to null. The EAG also criticised the inclusion of region as a variable for adjustment in the IPTW. To clarify, region was chosen as one of the key covariates to be included in the IPTW model based on expert opinion as there could be differences in treatment availability and healthcare practice that are related to patient's outcome across study sites. Due to consideration of the positivity assumption (no patients from the avapritinib cohort were from

		the UK site, one of the sites contributing data for the real-world study best available therapy [BAT] cohort), region (US vs. Europe) instead of study site was included as a covariate. In the analysis comparing avapritinib to cladribine in the 2L+ setting, region was not included in the IPTW model nor the IPTW-weighted Cox proportional hazards model because no patients in the cladribine cohort were from the US (violation of positivity). In the analysis comparing avapritinib to midostaurin in the 1L setting, region was included in the IPTW model. To test the robustness of the study against the choice of including region as a covariate in the IPTW model, Blueprint Medicines conducted a sensitivity analysis in the same subgroup comparing 1L 200mg avapritinib vs. 1L midostaurin without including region as one of the covariates in the IPTW model.[17] The adjusted hazard ratio (aHR) from the weighted Cox model was [redacted] (95% CI: [redacted], [redacted]; p<0.001), compared with an aHR of 0.14 (95% CI: [redacted], [redacted]; p<0.001) from the original analysis in which region was included in both the IPTW model and the weighted Cox model.[6,17] Therefore, the conclusion of improved OS in 1L 200mg avapritinib compared with 1L midostaurin was consistent regardless of whether region was included as a variable for adjustment. The stabilised weights applied in the IPTW and the propensity weight distributions before and after IPTW-weighting are presented in the additional evidence addendum provided alongside this response form, which demonstrate that there are no extreme weights for all the subgroup analyses of OS and DoT and that patients with similar characteristics are present across treatment groups, supporting valid causal comparisons. Table 2 summarises the results from the updated ECS IPTW analysis in the safety population. After adjusting for confounding factors, avapritinib maintained a substantial and significant reduction in the risk of death compared with 1L midostaurin ([redacted] reduction in risk of death; p<0.001) and 2L+ cladribine ([redacted] reduction in the risk of death vs. 2L+ cladribine; p=0.004).[6] Avapritinib also demonstrated prolonged median DoT compared with midostaurin at 1L (37.6 months vs. 11.6 months; p<0.001) and cladribine at 2L+ (24.0 months vs. 4.7 months; p<0.001).[6] For transparency, the adjusted hazard ratios (aHRs) derived from each cox-proportional hazards model are provided in Appendix B of the additional evidence addendum.

Table 2. Summary of results from ECS IPTW analyses (safety population)[6]

Subgroup	Outcome	Ava N	Mido/Clad N	Unadjusted HR (95% CI)	aHR (95% CI)
1L Ava vs. 1L midostaurin	OS	46	58 LOTs (58 patients)	[redacted]	[redacted]
	DoT	46	58 LOTs (58 patients)	[redacted]	[redacted]
2L+ Ava vs. 2L+ cladribine	OS	79	29 LOTs (27 patients)	[redacted]	[redacted]
	DoT	79	25 LOTs (24 patients)	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; aHR, adjusted hazard ratio; DoT, duration of treatment; ECS, external control study; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LOT, line of therapy; OS, overall survival.

In summary, the updated ECS IPTW analyses provide robust indirect treatment comparisons for avapritinib 200 mg against current standard of care, namely 1L midostaurin and 2L+ cladribine, using the largest and most recent trial data available for the avapritinib cohort. Outcomes from the analyses demonstrate that avapritinib has the potential to offer patients a much-needed and substantial improvement in survival outcomes across all lines of treatment and a significantly extended duration of treatment, which is indicative of prolonged PFS.

As described in Section B.2.9.2.2 of the company submission, the ECS IPTW could not provide comparative data on PFS, because PFS was not recorded in the retrospective real-world cohort. Even where time to progressive disease could be accurately determined in the real-world cohort, the progression criteria used in different centres was generally not consistent and different from those used in PATHFINDER, and as such, these could not have been applied retrospectively. Therefore, the revised base case uses DoT outcomes

		from the ECS IPTW as a proxy for PFS. To reduce the uncertainty associated with this assumption, the model also includes a scenario analysis which compared 1L avapritinib and 1L midostaurin using PFS outcomes derived from a matching-adjusted indirect comparison (MAIC) that used pooled PATHFINDER and EXPLORER data from the April 2021 data cut-off.[18] PFS outcomes for avapritinib vs. midostaurin in the MAIC (HR: [redacted]; 95% CI: [redacted]) were in line with the DoT outcomes in the updated ECS IPTW (HR: [redacted]; 95% CI: [redacted]), validating the assumption that the DoT outcomes derived from the ECW IPTW analyses are an appropriate proxy for PFS (see Issue 7).[6,18]
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Yes	The economic analysis has been updated with pooled PATHFINDER 2023 and EXPLORER 2023 data. Blueprint Medicine's acknowledges the EAG's concerns about the approach used to determine the PFS curves for both avapritinib and comparators and duration of treatment (DoT). The following data sources are used in the revised base case: • OS – pooled PATHFINDER 2023 and EXPLORER 2023 adjusted for IPTW from the ECS (safety population) (see issue 6 for more detail)[6] • PFS – pooled PATHFINDER 2023 and EXPLORER 2023 (Response Assessment Committee response-evaluable [RAC-RE] population) for avapritinib[3] and DoT from ECS IPTW for comparator.[6] Progression was not captured in the safety population as mIWG-MRT-ECNM criteria was used to capture progressive disease in RAC-RE population (see issue 7 for more detail). • DoT – pooled PATHFINDER 2023 and EXPLORER 2023 adjusted for IPTW from the ECS (safety population) (see issue 8 for more detail).[6] Clinical experts deemed the ECS data as an appropriate source to inform avapritinib DoT (see issue 8 for more detail).

Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations	Yes	The EAG commented on the immaturity of the survival data (2022 data cut-off) to inform extrapolations in the model, with median OS not reached in either population.[1] The company have updated the economic analysis using the latest data available from pooled PATHFINDER 2023 and EXPLORER 2023. This provides an additional 10 months of follow up compared with PATHFINDER 2022

		the OS results are consistent with PATHFINDER 2022, although median OS has not been reached. In patients who had not received prior systemic therapy (1L) Kaplan Meier (KM) estimates for OS at 24 months were 88.5% (95% CI: 77.9%, 99.1%) and [redacted] for PATHFINDER 2022 and pooled 2023, respectively. In patients who had received prior systemic therapy (2L+) KM estimates for OS at 24 months were 73.6% (95% CI: 62.3%, 84.9%) and [redacted] for PATHFINDER 2022 and pooled 2023, respectively.[3,19] The company's base case OS extrapolation predicts [redacted] and [redacted] of patients to be alive at 24 months for 1L and 2L+ populations, respectively. The modelled extrapolations are concurrent with that observed in the pooled 2023 KM estimates of [redacted] and [redacted] for 1L and 2L+ populations, respectively. The latest pooled 2023 data cut-off provides further certainty to the company's modelled extrapolations in predicting OS outcomes. In addition, the company has provided scenarios testing optimistic and pessimistic survival extrapolations (see Table 10 and Table 11. The optimistic scenarios were associated with [redacted] in the ICER and pessimistic scenarios were associated with [redacted] in the ICER, when compared to 1L midostaurin.
Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS	Yes	The EAG commented on the inconsistency in the PFS approach used for avapritinib and the comparators and inconsistent survival outcomes between the OS safety and RAC-RE population.[1] The ECS IPTW could not provide comparative data on PFS because the outcome was not recorded in the retrospective real-world cohort. Even where time to progressive disease could be accurately determined, the response to treatment, including progression criteria, used in different centres were not consistent with those used in PATHFINDER and EXPLORER. This is because published response criteria have evolved over the time period of the real-world data collection and none were officially established as a global standard or consistently applied, even across expert centres.[20-22] On the other hand, the assessment of progressive disease and PFS in the clinical trials for

		avapritinib were consistently made using mIWG-MRT-ECNM criteria, which can only be assessed in the RAC-RE population, and therefore used in the economic analysis.[3] In the pooled PATHFINDER and EXPLORER 2023 analysis, PFS estimates in the RAC-RE population for both 1L and 2L+ patients had reached its median of [redacted] months and [redacted] months, respectively, addressing the EAG's comments on the immaturity of the PFS curves and resolving inconsistencies with OS data from the safety population.[3] Blueprint Medicines believes using data directly from the clinical trials to inform PFS outcomes provides the most robust evidence available for avapritinib since trial results are generalisable to the UK and long-term survival benefits will be capped at 7.5 years (see issue 9). To minimise uncertainty in estimating comparator PFS, the following scenarios are presented within Table 10 and Table 11): • MAIC analysis to inform comparator PFS (based on pooled PATHFINDER and EXPLORER 2021 data cut-offs)[18] • EAG preferred assumption: DoT as a proxy for PFS for avapritinib (using IPTW-adjusted DoT)[6] • DoT as a proxy for PFS for avapritinib (using compassionate use programme (CUP) to DoT)[23] • Applying the OS HR (results from pooled 2023 ECS IPTW) for both 1L and 2L+ patients to inform comparator PFS[6] The scenarios were associated with a [redacted] in the ICER (MAIC PFS), a [redacted] in the ICER (DoT as proxy for PFS using IPTW), a [redacted] in the ICER (DoT as proxy for PFS using CUP), and

		[redacted] in the ICER (2023 OS IPTW HR) respectively, when compared to the company's updated base case (versus 1L midostaurin). *Please note, as avapritinib dominates midostaurin, the directional change of the ICER is nuanced (an improvement in the cost benefit and a worsening of clinical outcomes, both causes a decrease in the ICER).*
Issue 8: Source of evidence used to inform time on treatment in the model	Yes	The revised base case uses the updated ECS IPTW analysis to inform DoT, aligning with OS outcomes in the model, EAG preferred assumptions and feedback from consultant haematologists. This is a conservative assumption when considering real-world evidence for avapritinib, with substantially shorter median DoT observed in patients treated with avapritinib in the CUP compared with estimates from the ECS IPTW analysis (16.6 months vs. [redacted] months).[6,23] DoT data from the CUP (N=13) was explored in a scenario analysis and is considered reflective of treatment with avapritinib in clinical practice. Patients in the CUP were generally high-risk despite most not receiving any prior systemic therapy (76.9%), with a large proportion of patients having SM-AHN (84.6%) and 61.5% harbouring high-risk mutations.[23] The differences observed between trial data and the CUP data emphasises the complexity and heterogeneity of the AdvSM population. In addition, patients treated as part of the CUP did not follow strict trial protocols like in PATHFINDER, which is more reflective of clinical practice.[23] The scenario analysis from the CUP is likely to be reflective of high-risk patients who would receive avapritinib at 1L and highlights the importance of considering a range of potential treatment durations to inform decision-making to account for the heterogeneity in AdvSM.[23] The revised base case, using pooled 2023 ECS IPTW data to inform DoT, has a [redacted] on the ICER, when compared to the company's original base (Table 3). Full time on treatment curves are presented in the additional evidence addendum to technical engagement, see Section 3.1.4.2.1. **Table 3. Summary of DoT data**

		<table><tr><th>Data source</th><th>DoT avapritinib from data source median (months)</th><th>Proportion on treatment at 7.5 years</th><th>ICER change from company base case</th></tr><tr><td colspan="4">1L versus midostaurin</td></tr><tr><td>CUP (company old base case)[23]</td><td>16.6</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Pooled PATHFINDER 2023 and EXPLORER 2023 ECS IPTW[6] (Company revised base case and EAG base case)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>PATHFINDER 2022[19]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td colspan="4">2L+ versus cladribine</td></tr><tr><td>CUP (company old base case)[23]</td><td>16.6</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Pooled PATHFINDER 2023 and EXPLORER 2023 ECS IPTW[6] (Company revised base case and EAG base case)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>PATHFINDER 2022[19]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table> Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; CUP, compassionate use program; DoT, duration of treatment; EAG, external assessment group; ECS, external control study; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability of treatment weighting.
Issue 9: Uncertain duration of treatment benefit for avapritinib	Yes	The EAG explored the interplay between the survival parameters, OS and PFS, and duration of treatment benefit and time on treatment. They stated that the company's assumption of 5 years for duration of response in the model is reasonable. However, when adjusting assumptions to the EAGs preferred methods for PFS (using DoT as a proxy for PFS for avapritinib and comparators), the EAG acknowledges that a 5-year duration of treatment benefit may be considered

pessimistic as approximately [redacted]% of patients remain on treatment at 5 years using the EAGs preferred assumptions.[1]

Blueprint Medicines has updated the base case assumptions aligning with EAG approach, using pooled 2023 ECS IPTW data to inform DoT.[6] As mentioned in the EAG report, it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes. Therefore, the company have updated their initial treatment benefit to 7.5 years to reflect the longer treatment duration, which is in line with expectations from UK consultant haematologists.

In the company's updated base case, approximately [redacted] of patients remain on treatment at 7.5 years. In PATHFINDER 2023, of patients who demonstrated an ORR to avapritinib, [redacted]% maintained this response as of the data cut-off, with median follow-up >3 years, compared with the previous data cut-off of 86.7% with a median follow-up of >2 years.[5] Therefore, a treatment duration benefit of 7.5 years was considered appropriate for the company base case.

As the duration of treatment effect is increased, there is a significant improvement in the ICER (Table 4).

Table 4. Summary of the impact of scenario analyses on survival parameters on the proportion of patients on treatment at 7.5 years

Analysis	Proportion of patients on treatment at 7.5 years in the model	DoT settings	PATHFINDER 2023 DOR rate at 54 months, KM estimate, % (95% CI)	Pooled PATHFINDER 2023 and EXPLORER 2023 DOR rate at 54 months, KM estimate, % (95% CI)

		<table><tr><td>Company updated base case</td><td>[redacted]</td><td>PATHFINDER & EXPLORER 2023 ECS IPTW[6]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td></tr><tr><td>EAG base case</td><td>[redacted]</td><td>PATHFINDER 2022 ECS IPTW[24-26]</td></tr></table> Abbreviations: CI, confidence interval; CUP, compassionate use program; DoT, duration of treatment; DOR, duration of response; EAG, external assessment group; ECS, external control study; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.
Issue 10: Exclusion of subsequent therapy	No	The EAG highlighted that subsequent treatment costs are not used in the company model. There are no data to inform economic analyses on subsequent treatment use and post-progression survival outcomes. Feedback received from UK consultant haematologists suggest that subsequent treatment received after avapritinib 1L would be cladribine (30-35%) and AML like treatment (50%). There are no further data to support a modelling scenario for costing subsequent treatment. Therefore, the company have run a scenario informed by KOL feedback on the impact of subsequent treatment costs on the model. The impact on cost-effectiveness is a [redacted] in the ICER.
Issue 11: Uncertainty in the progression-free (PF) and progressed disease (PD) health state utility values (HSUV)	Yes	The EAG were concerned about the limited data available from PATHFINDER to inform the PF utility value. The latest 2023 data cut-offs provides pooled HRQoL estimates with increased number of observations to inform the PF HSUV (see company additional evidence addendum, Section 3.1.4.4).[3] Updated values are similar to the company's original submission, which align with the UK clinical feedback received during the initial submission (see Table 5). The updated HRQoL data had a minimal impact on the results, with a [redacted] in the ICER (Table 7). **Table 5. HSUV in company model** <table><tr><th>Health state</th><th>Original company base case utility value</th><th>Updated company base case utility value</th></tr></table>

		PF (1L) [redacted] [redacted] **PD (1L)** [redacted] [redacted] **PF (2L+)** [redacted] [redacted] **PD (2L+)** [redacted] [redacted] Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; HSUV, health state utility value; PD, progressed disease; PF, progression free. Similar to the original CS, there were still only a few observations for patients with the progressive disease and the sample size was deemed too small to inform decision making. Therefore, to derive PD utility values the methodology in the CS was replicated. Although EAG are concerned about the derivation of the PD value, there will be no long-term impact because patients return to comparator arm efficacy after 7.5 years. Impact on varying HSUVs is explored in the one-way sensitivity analysis, see cost-effectiveness results below.

Additional issues

No other key issues identified.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Following the EAG clarification stage, a revised patient access scheme (PAS) was submitted for avapritinib with a simple fixed price discount of [redacted] Results for PAS price for avapritinib have been included in the cost-effectiveness analysis. There is a commercial arrangement for midostaurin, it is confidential and therefore the list price is used for midostaurin in the company analyses.

Table 4. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issues 5, 6, 7, 8, 9 and 11	• PATHFINDER 2022 ECS IPTW informing OS • CUP data informing avapritnib DoT • Unweighted ECS analysis informing midostaurin DoT • PATHFINDER 2022 RAC-RE population informing avapritinib PFS • PATHFINDER 2022 data informing PF HRQoL • PATHFINDER 2022 data informing AEs	• Pooled PATHFINDER and EXPLORER 2023 ECS IPTW informing OS and DoT • Pooled PATHFINDER and EXPLORER 2023 RAC-RE population informing avapritinib PFS • Pooled PATHFINDER and EXPLORER 2023 data informing PF HRQoL • Pooled PATHFINDER 2023 and EXPLORER 2023 informing AEs • Duration of treatment benefit 7.5 years	**ICER versus 1L midostaurin:** Original ICER: [redacted] Updated ICER: [redacted] **ICER versus 2L+ cladribine:** Original ICER: [redacted] Updated ICER: [redacted] The updated company base case analysis is associated with a [redacted] decrease in the ICER compared to the original company base case, versus midostaurin (improves) and a [redacted] decrease (improves) compared to cladribine.

	• Duration of treatment benefit: 5 years		
Company's base case following technical engagement (or revised base case) at PAS price	**QALYs versus 1L midostaurin:** Incremental QALYs: 2.95 **QALYs versus 2L+ cladribine:** Incremental QALYs: 1.77	**Costs versus 1L midostaurin:** Incremental costs: [redacted] **Costs versus 2L+ cladribine:** Incremental costs: [redacted]	ICER versus 1L midostaurin: [redacted] ICER versus 2L+ cladribine [redacted]

* Please note, as avapritinib dominates midostaurin, the directional change of the ICER is nuanced (an improvement in the cost benefit and a worsening of clinical outcomes, both cause a decrease in the ICER).

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; AE, adverse event; CUP, compassionate use program; DoT, duration of treatment; ECS, external control study; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; OS, overall survival, QALY, quality-adjusted life year; RAC-RE, Response Assessment Committee response-evaluable.

Table 6. Company's revised base case cost-effectiveness results at PAS price following TE

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	7.46	5.01	[redacted]	4.30	2.95	[redacted]	[redacted]
Midostaurin	[redacted]	3.16	2.06					
Comparison B: Avapritinib vs cladribine, 2L+								
Avapritinib	[redacted]	5.12	3.19	[redacted]	2.34	1.77	[redacted]	[redacted]
Cladribine	[redacted]	2.79	1.42					

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; TE, technical engagement.

Table 7. Company's revised discounted base case NHB and NMB results at PAS price following TE

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB (WTP £36,000)	NHB (WTP £30,000)	NMB (WTP £36,000)	NMB (WTP £30,000)
Comparison A: Avapritinib vs midostaurin, 1L								
Avapritinib	[redacted]	5.01	[redacted]	2.95	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	2.06						
Comparison B: Avapritinib vs cladribine, 2L+								
Avapritinib	[redacted]	3.19	[redacted]	1.77	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	1.42						

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TE, technical engagement; WTP, willingness-to-pay.

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Table 8 presents the probabilistic results for the 1L avapritinib versus midostaurin analysis. The probabilistic results are aligned to the base case deterministic results, and the cost effectiveness plane (Figure 1) shows results to be tightly clustered around the base case results, implying the model results to be subject to a reasonable level of uncertainty. The cost-effectiveness acceptability curve shows avapritinib to be cost-effective at every willingness to pay threshold (Figure 2).

Table 8. Probabilistic results for 1L avapritinib versus midostaurin

	Cost (£)			QALYs			ICER
	Avapritinib	Midostaurin	Incremental	Avapritinib	Midostaurin	Incremental	(£/QALY)
Base case	[redacted]	[redacted]	[redacted]	5.01	2.06	2.95	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	4.88	2.01	2.87	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	4.25	1.78	2.45	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	5.44	2.26	3.26	[redacted]

Abbreviations: 1L, first line of therapy; CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 1. Cost-effectiveness plane for 1L avapritinib versus midostaurin

Abbreviations: 1L, first line of therapy; CE, cost-effectiveness; QALY, quality-adjusted life year.

Figure 2.Cost-effectiveness acceptability curve for 1L avapritinib versus midostaurin

Abbreviations: 1L, first line of therapy; CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Table 9 presents the probabilistic results for the 2L+ avapritinib versus cladribine analysis. The probabilistic results are aligned to the base case deterministic results, and the cost effectiveness plane (Figure 3) shows results to be tightly clustered around the base case results, implying the model results to be subject to a reasonable level of uncertainty. The cost-effectiveness acceptability curve shows avapritinib to have a 50% chance of being cost-effective at a willingness to pay threshold of £50k, rising to 100% chance at a willingness to pay threshold of £190k. (
Figure 4).

Table 9. Probabilistic results for 2L+ avapritinib versus cladribine

	Cost (£)			QALYs			ICER (£/QALY)
	Avapritinib	Cladribine	Incremental	Avapritinib	Cladribine	Incremental	
Base case	[redacted]	[redacted]	[redacted]	3.19	1.42	1.77	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	3.17	1.42	1.75	[redacted]
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	2.88	1.20	1.50	[redacted]
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	3.47	1.64	2.01	[redacted]

Abbreviations: 2L+, second or later line of therapy; CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 3. Cost-effectiveness plane for 2L+ avapritinib versus cladribine

Abbreviations: 2L+, second or later line of therapy; CE, cost-effectiveness; QALY, quality-adjusted life year.

Figure 4. Cost-effectiveness acceptability curve for 2L+ avapritinib versus cladribine

Abbreviations: 2L+, second or later line of therapy; CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Deterministic sensitivity analysis

Updated DSA provided in line with methods used in original CS (see CS, Section B.3.12.2). Results for the ten most influential parameters identified by univariate sensitivity analysis are presented in Figure 5 for the 1L analysis vs. midostaurin and Figure 6 for the 2L+ analysis vs. cladribine. The OWSA's showed similar trends to the original CS, with the discount rates (for both costs and outcomes) and HRQoL data being shown to be the most sensitive parameters to variation.

Figure 5. Tornado diagram for OWSA for 1L avapritinib versus midostaurin

Abbreviations: 1L, first line of therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year.

Figure 6. Tornado diagram for OWSA for 2L+ avapritinib versus cladribine

Abbreviations: 2L+, second or later line of therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year.

Scenario analysis

Various structural assumptions were examined, encompassing both optimistic and pessimistic exploratory analyses Table 10 and Table 11 provides a summary and results of the different scenarios explored for the different analyses for 1L vs. midostaurin and 2L+ vs. cladribine respectively.

The analyses tested replicate the scenarios tested in the EAG report, with updates made concerning the optimistic and pessimistic scenarios for the updated data cut.

Table 10. Scenario analysis versus 1L midostaurin

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £30,000)
Updated base case (2022 data-cut)			[redacted]	[redacted]
Updated base case (2023 data-cut)			[redacted]	[redacted]
DoT	DoT sourced from pooled PATHFINDER & EXPLORER 2023 ECS IPTW	DoT sourced from RWE (CUP for avapritinib, unweighted ECS for midostaurin)	[redacted]	[redacted]
PFS methodology for avapritinib	PFS sourced from pooled PATHFINDER 2023 & EXPLORER 2023 (avapritinib)	**EAG scenario 2** DoT as proxy for PFS of avapritinib using pooled PATHFINDER & EXPLORER 2023 ECS IPTW	[redacted]	[redacted]
PFS methodology for comparator	Comparator PFS equivalent to DoT	PFS MAIC 2021	[redacted]	[redacted]
		Applying the OS HR (resulting from the IPTW ITC)	[redacted]	[redacted]
OS extrapolations	OS extrapolation for avapritinib: generalised gamma	**EAG scenario 3a** Pessimistic OS extrapolation for avapritinib: exponential	[redacted]	[redacted]
		EAG scenario 3b Optimistic OS extrapolation for avapritinib: Gompertz	[redacted]	[redacted]
	OS extrapolation for midostaurin: exponential	**EAG scenario 3c** Pessimistic OS extrapolation for midostaurin: gamma	[redacted]	[redacted]
		EAG scenario 3d	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £30,000)
		Optimistic OS extrapolation for midostaurin: log logistic		
Duration of treatment effect	Duration of TE of 7.5 years	Duration of TE of 5 years	[redacted]	[redacted]
		EAG scenario 5 Duration of TE of 10 years	[redacted]	[redacted]
		EAG scenario 6 Duration of TE of lifetime	[redacted]	[redacted]
Interaction between survival outcomes, time on treatment, and duration of treatment effect	OS extrapolation for avapritinib: generalised gamma midostaurin: exponential DoT extrapolation for avapritinib: exponential midostaurin: log normal Duration of TE of 7.5 years	**EAG scenario 7a** **Small TE jointly (duration of TE of 5 years)** Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic DoT avapritinib (generalised gamma) + optimistic DoT midostaurin (generalised gamma)	[redacted]	[redacted]
		EAG scenario 7b **Large TE jointly (duration of TE of 5 years)** Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (gamma) Optimistic DoT avapritinib (log logistic) + pessimistic DoT midostaurin (exponential)	[redacted]	[redacted]
		EAG scenario 8a **Small TE jointly (duration of TE of 7.5 years)** Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic DoT avapritinib (generalised gamma) + optimistic DoT midostaurin (generalised gamma)	[redacted]	[redacted]
		EAG scenario 8b	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £30,000)
		Large TE jointly (duration of TE of 7.5 years) Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (gamma) Optimistic DoT avapritinib (log logistic) + pessimistic DoT midostaurin (exponential)		
		EAG scenario 9a **Small TE jointly (duration of TE of 10 years)** Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic DoT avapritinib (generalised gamma) + optimistic DoT midostaurin (generalised gamma)	[redacted]	[redacted]
		EAG scenario 9b **Large TE jointly (duration of TE of 10 years)** Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (gamma) Optimistic DoT avapritinib (log logistic) + pessimistic DoT midostaurin (exponential)	[redacted]	[redacted]
		EAG scenario 10a **Small TE jointly (duration of TE of lifetime)** Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log logistic) Pessimistic DoT avapritinib (generalised gamma) + optimistic DoT midostaurin (generalised gamma)	[redacted]	[redacted]
		EAG scenario 10b **Large TE jointly (duration of TE of lifetime)** Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (gamma)	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £30,000)
		Optimistic DoT avapritinib (log logistic) + pessimistic DoT midostaurin (exponential)		
Utility value	PF utility of 0.733	**EAG scenario 11** PF utility of 0.7	[redacted]	[redacted]
Subsequent therapy	Excluded	Included	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; DoT, duration of treatment; EAG, external assessment group, NMB, net monetary benefit; OS, overall survival; PF, progression-free; PFS, progression-free survival; TE, treatment effect.

Table 11. Scenario analysis versus cladribine 2L+

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
Updated base case (2022 data-cut)			[redacted]	[redacted]
Updated base case (2023 data-cut)			[redacted]	[redacted]
DoT	DoT sourced from pooled PATHFINDER & EXPLORER 2023 ECS IPTW	DoT sourced from RWE (CUP for avapritinib, unweighted ECS for cladribine)	[redacted]	[redacted]
PFS methodology for avapritinib	PFS sourced from pooled PATHFINDER 2023 & EXPLORER 2023 (avapritinib)	**EAG scenario 2** DoT as proxy for PFS of avapritinib using pooled PATHFINDER & EXPLORER 2023 ECS IPTW	[redacted]	[redacted]
		PFS MAIC 2021	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
PFS methodology for comparator	Comparator PFS equivalent to DoT	Applying the OS HR (resulting from the IPTW ITC)	[redacted]	[redacted]
OS extrapolations	OS extrapolation for avapritinib: exponential	**EAG scenario 3a** Pessimistic OS extrapolation for avapritinib: exponential	[redacted]	[redacted]
		EAG scenario 3b Optimistic OS extrapolation for avapritinib: Gompertz	[redacted]	[redacted]
	OS extrapolation for cladribine: exponential	**EAG scenario 3c** Pessimistic OS extrapolation for cladribine: exponential	[redacted]	[redacted]
		EAG scenario 3d Optimistic OS extrapolation for cladribine: Gompertz	[redacted]	[redacted]
Duration of treatment effect	Duration of TE of 7.5 years	Duration of TE of 5 years	[redacted]	[redacted]
		EAG scenario 5 Duration of TE of 10 years	[redacted]	[redacted]
		EAG scenario 6 Duration of TE of lifetime	[redacted]	[redacted]
Interaction between survival outcomes, time on treatment, and duration of treatment effect	OS extrapolation for avapritinib: exponential cladribine: exponential DoT extrapolation for avapritinib: Gompertz cladribine: exponential	**EAG scenario 7a** **Small TE jointly (duration of TE of 5 years)** Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic DoT avapritinib (exponential) + optimistic DoT cladribine (log logistic)	[redacted]	[redacted]
		EAG scenario 7b **Large TE jointly (duration of TE of 5 years)**	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
	Duration of TE of 7.5 years	Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (exponential) Optimistic DoT avapritinib (Gompertz) + pessimistic DoT cladribine (exponential)		
		EAG scenario 8a **Small TE jointly (duration of TE of 7.5 years)** Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic DoT avapritinib (exponential) + optimistic DoT cladribine (log logistic)	[redacted]	[redacted]
		EAG scenario 8b **Large TE jointly (duration of TE of 7.5 years)** Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (exponential) Optimistic DoT avapritinib (Gompertz) + pessimistic DoT cladribine (exponential)	[redacted]	[redacted]
		EAG scenario 9a **Small TE jointly (duration of TE of 10 years)** Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic DoT avapritinib (exponential) + optimistic DoT cladribine (log logistic)	[redacted]	[redacted]
		EAG scenario 9b **Large TE jointly (duration of TE of 10 years)** Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (exponential) Optimistic DoT avapritinib (Gompertz) + pessimistic DoT cladribine (exponential)	[redacted]	[redacted]

Variable	Base case	Scenario	ICER (£/QALY)	NMB (WTP £36,000)
		EAG scenario 10a **Small TE jointly (duration of TE of lifetime)** Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic DoT avapritinib (exponential) + optimistic DoT cladribine (log logistic)	[redacted]	[redacted]
		EAG scenario 10b **Large TE jointly (duration of TE of lifetime)** Optimistic OS avapritinib (Gompertz) + pessimistic OS cladribine (Exponential) Optimistic DoT avapritinib (Gompertz + pessimistic DoT cladribine (Exponential)	[redacted]	[redacted]

Abbreviations: 2L+, second or later line of therapy; DoT, duration of treatment; EAG, external assessment group, NMB, net monetary benefit; OS, overall survival; PF, progression-free; PFS, progression-free survival; TE, treatment effect.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Technical engagement additional evidence addendum

14 June 2024

File name	Version	Contains confidential information	Date
ID3770 Avapritinib Technical Engagement Additional Evidence Addendum [CON]	vFINAL	Yes	14 June 2024

Contents

List of tables

List of figures

1 Introduction

In response to technical engagement, Blueprint Medicines is providing this addendum with longer-term (≥3 years) evidence supporting the clinical value of avapritinib. This longer-term evidence is based on:

- Updated data from the PATHFINDER trial (latest data cut-off: 15 September 2023)[1]
- Updated pooled analyses from both the EXPLORER trial (latest data cut-off: 19 January 2023) and the PATHFINDER trial (latest data cut-off: 15 September 2023)[2]
- The updated external control study (ECS) using the latest pooled PATHFINDER and EXPLORER data to compare first-line (1L) treatment with avapritinib to 1L midostaurin, and second-line and beyond (2L+) avapritinib with 2L+ cladribine.[3]

In line with the scope of this appraisal, this document only includes data for avapritinib from patients who received a starting dose of 200 mg.

Additionally, Blueprint Medicines has updated its economic base case and scenario analyses to revise key assumptions, such as data sources informing duration on treatment (DoT) and duration of treatment benefit. The economic analysis includes the latest data cut-offs from the pooled PATHFINDER 2023 and EXPLORER 2023 analyses and updated ECS IPTW analyses.[2,3]

Table 1 provides an outline of the sections of the addendum which provide supplementary information to address the key issues raised in the EAG report.

Table 1. Summary of the EAG issues addressed by the provided additional evidence

EAG issues	Summary of company approach	Justification
Issue 3: Limitations of the effectiveness evidence	To address uncertainty in the clinical evidence due to data immaturity, Blueprint Medicines has provided additional evidence with longer-term (≥3 years) evidence supporting the clinical value of avapritinib.	See Section 2.1
Issue 4: Limitations of the indirect treatment comparisons	An updated ECS has been provided, with data for the avapritinib cohort derived from a pooled population of patients receiving an initial dose of 200 mg from the latest data cut-offs for PATHFINDER and EXPLORER.	See Section 2.2
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Updated from the original company base case. The economic analysis has been updated with pooled PATHFINDER 2023 and EXPLORER 2023 and adjustments for IPTW for the comparisons from the ECS used to inform OS and DoT in the CEM.	See section 3.1
Issue 6: Immaturity of the OS data used in the extrapolations	Updated from original company base case. The economic analysis has been updated with the most recent data cut-off from pooled PATHFINDER 2023 and EXPLORER 2023. Providing an additional 10 months of follow up compared with PATHFINDER 2022.	See section 3.1.4.1

EAG issues	Summary of company approach	Justification
Issue 7: Limited availability of PFS and use of DoT as a proxy for PFS	Updated from the original company base. Pooled PATHFINDER 2023 and EXPLORER 2023 RAC-RE population reached its median in both populations (1L and 2L+) and used in the company base case. Alternative approaches have been explored in estimating comparator PFS.	See section 3.1.4.3
Issue 8: Source of evidence used to inform DoT in model	Updated from the original company base case. Avapritinib time on treatment evidence is informed by pooled 2023 ECS IPTW data, aligned with EAG preferred base case. Additional scenarios have been provided using data from the compassionate use programme (CUP) real world evidence and DoT from unweighted ECS (BLU-285-2405) for comparators.	See section 3.1.4.2
Issue 11: Uncertainty in the progression-free (PF) and progressed disease health state utility values	Updated from the original company base case. Pooled PATHFINDER 2023 and EXPLORER 2023 health-related quality of life (HRQoL) data available for progression free health state.	See section 3.1.4.4

Abbreviations: EAG, evidence assessment group; DoT, duration of treatment; HRQoL, health-related quality of life; progression-free (PF), OS, overall survival; PFS, progression free survival; ECS, external control study; IPTW, inverse probability of treatment weights; RAC-RE, Response Assessment Committee Response-Evaluable

2 Clinical data

2.1 PATHFINDER and EXPLORER (Issue 3)

The detailed study designs of EXPLORER (Study 285-2101) and PATHFINDER (Study 285-2202) were previously outlined in the initial company's submission (Document B). As of the latest data cut-offs in EXPLORER (19 January 2023) and PATHFINDER (15 September 2023), a total of 125 patients have initiated avapritinib at a daily dose of 200 mg (20 of 69 patients in EXPLORER and 105 of 107 patients in PATHFINDER).[1,2]

Median follow-up in patients in PATHFINDER as of the data cut-off was 38 months, providing an additional 12 months of follow-up data compared with the previous data cut-off (September 2022).[1,4] For the pooled analysis, as of the latest data cut-offs for PATHFINDER and EXPLORER, the median follow-up was 36 months, providing an additional 18 months of follow-up data compared with the previous pooled analysis (April 2021).[2,5]

2.1.1 Patient disposition and baseline characteristics

2.1.1.1 Patient disposition

A summary of patient disposition in PATHFINDER alone and PATHFINDER and EXPLORER (pooled) is provided in Table 2.

As of the data cut-off, of the 105 patients treated with 200 mg of avapritinib in PATHFINDER, [redacted] have discontinued treatment and [redacted] have discontinued from the study.[1] Primary reasons for study discontinuation included death ([redacted] patients) and withdrawal of consent ([redacted] patients), while primary reasons for treatment discontinuation included disease progression ([redacted] patients), adverse events (AEs) ([redacted] patients, including [redacted] that were assessed as treatment-related by the Investigators), withdrawal of consent ([redacted] patients), and sponsor decision ([redacted] patients).[1]

In PATHFINDER and EXPLORER, of the 125 patients treated with 200 mg of avapritinib, [redacted] have discontinued treatment and [redacted] have discontinued from the studies.[2] Primary reasons for study discontinuation included death ([redacted] patients) and withdrawal of consent ([redacted] patients), while primary reasons for treatment discontinuation included disease progression ([redacted] patients), AEs ([redacted] patients, including [redacted] with AEs assessed as treatment-related by the Investigators), withdrawal of consent ([redacted] patients), and sponsor decision ([redacted] patients).[2]

Table 2. Patient disposition in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Discontinued from treatment, n (%)	[redacted]											
Continuing on treatment, n (%)	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Discontinued from study, n (%)	[redacted]											
Reasons for discontinuation of treatment, n (%)												
Disease progression	[redacted]											
AE(s)	[redacted]											
Treatment-related AE(s)	[redacted]											
Death	[redacted]											
Lost to follow-up	[redacted]											
Protocol deviation	[redacted]											
Withdrew consent	[redacted]											
Pregnancy	[redacted]											
Investigator's decision	[redacted]											
Administrative/ other	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Sponsor decision	[redacted]											
Non-compliance	[redacted]											
Reasons for discontinuation of study, n (%)												
Disease progression	[redacted]											
AE(s)	[redacted]											
Death	[redacted]											
Lost to follow-up	[redacted]											
Protocol deviation	[redacted]											
Withdrew consent	[redacted]											
Pregnancy	[redacted]											
Investigator's decision	[redacted]											
Administrative/ other	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Initiation of another antineoplastic therapy	[redacted]											
Sponsor decision	[redacted]											

Abbreviations: 1L, patients who have not received prior systemic therapy; 2L+, patients who have received prior systemic therapy; AE, adverse event; RAC-RE; Response Assessment Committee response-evaluable.
The safety population includes all patients in the RAC-RE population. The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.
Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.1.2 Baseline characteristics

A summary of patient baseline characteristics in PATHFINDER alone and PATHFINDER and EXPLORER (pooled) as of the latest data cut-offs is provided in Table 3.[1,2] The baseline characteristics are broadly similar between patients in both analyses. There were slightly higher proportions of prior midostaurin use, prior cladribine use and females in the pooled analysis compared to PATHFINDER alone (Table 3).

Table 3. Baseline characteristics of patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER

Characteristic	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Age, median years (range)	[redacted]											
Female, n (%)	[redacted]											
ECOG performance status, n (%)												
0	[redacted]											
1	[redacted]											
2	[redacted]											
3	[redacted]											
AdvSM subtype, n												
ASM	[redacted]											

Characteristic	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
SM-AHN	[redacted]											
MCL	[redacted]											
***KIT* mutation exon 17, n (%)**	[redacted]											
KIT D816V, n (%)	[redacted]											
***KIT* D816V VAF, median % (range)**	[redacted]											
S/A/R mutation, n (%)	[redacted]											
BM mast-cell burden, median % (range)	[redacted]											

Characteristic	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Serum tryptase level, median ng/mL (range)	[redacted]											
Spleen volume, median mL (range)	[redacted]											
Prior systemic therapy*, n (%)												
Midostaurin	[redacted]											
Cladribine	[redacted]											
Interferon alpha	[redacted]											
Imatinib	[redacted]											
Dasatinib	[redacted]											
Hydroxycarbamide	[redacted]											

Characteristic	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigational antineoplastic drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon alpha-2a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem cells nos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	Safety population			RAC-RE population			Safety population			RAC-RE population		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=51)	1L (n=30)	All (n=81)	2L+ (n=79)	1L (n=46)	All (N=125)	2L+ (n=63)	1L (n=35)	All (n=98)
Protein kinase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Purine analogues	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, patients who have not received prior systemic therapy; 2L+, patients who have received prior systemic therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; NR, not reported; RAC-RE, response assessment committee response-evaluable; S/A/R, *SRSF2*/*ASXL1*/*RUNX1* gene panel; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; VAF, variant allele fraction. *Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Note: The safety population includes all the patients in the RAC-RE population.
Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.
Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.2 Efficacy results

2.1.2.1 Response to treatment according to mIWG-MRT-ECNM criteria

As of the September 2023 cut-off for PATHFINDER, avapritinib maintained high levels of efficacy in patients with AdvSM who initiated avapritinib at a dose of 200 mg, consistent with the previous data cut-off (September 2022).[1,4] Specifically, an ORR of [redacted]% (95%

CI:[redacted], [redacted]) was observed, including a complete remission (CR) rate of [redacted]% and complete remission with partial haematologic recovery (CRh) rate of [redacted]% (Table 4).[1] ORR was higher in 1L patients ([redacted]%) compared with 2L+ patients ([redacted]%) in PATHFINDER.[1] Similar response rates were observed in the pooled PATHFINDER and EXPLORER analysis (ORR, [redacted]%; CR rate, [redacted]%, CRh rate, [redacted]%) compared with PATHFINDER alone (Table 4).[2]

Table 4. Response to therapy per mIWG-MRT-ECNM criteria in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (RAC-RE population)

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	(n=81)	ASM (n=14)	SM-AHN (n=63)	MCL (n=21)	2L+ (n=63)	1L (n=35)	(n=98)
ORR,* n (%) [95% CI]	[redacted]											
CR, n (%)	[redacted]											
CRh, n (%)	[redacted]											
PR, n (%)	[redacted]											
Clinical improvement, n (%)	[redacted]											
Duration of response†												
Median DOR, months (95% CI)	[redacted]											
Censored, n (%)	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	(n=81)	ASM (n=14)	SM-AHN (n=63)	MCL (n=21)	2L+ (n=63)	1L (n=35)	(n=98)
DOR rate at 12 months, KM estimate, % (95% CI)	[redacted]											
DOR rate at 24 months, KM estimate, % (95% CI)	[redacted]											
DOR rate at 36 months, KM estimate, % (95% CI)	[redacted]											
DOR rate at 48 months, KM estimate, % (95% CI)	[redacted]											
DOR rate at 54 months, KM estimate, % (95% CI)	[redacted]											
Time to response												
Time to response (ORR), months, median (range)	[redacted]											
Time to CR or CRh, months, median (range)	[redacted]											

Abbreviations: 1L, patients who had not received prior systemic therapy; 2L+, patients who had received prior systemic therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, confidence interval; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; DOR, duration of response; KM, Kaplan-Meier; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL, mast cell leukaemia; NR, not reported; NE, not evaluable; ORR, overall response rate; PR, partial remission; RAC-RE, response assessment committee response-evaluable; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm.

*ORR is the sum of CR, CRh, PR, and clinical improvement.

†The last available follow-up was 54 months.

The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.2.2 Overall survival

Overall survival in PATHFINDER patients (safety population) who initiated avapritinib at a dose of 200 mg is presented in Figure 1. As of the data cut-off, median OS has not yet been reached in this population, [redacted] of 105 patients were alive and the Kaplan-Meier (KM) estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[1]

Overall survival in PATHFINDER and EXPLORER patients (safety population) who initiated avapritinib at a dose of 200 mg is presented in

Figure 2. As of the latest data cut-offs, median OS has not yet been reached in this population, [redacted] of 125 patients were alive and the KM estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[2]

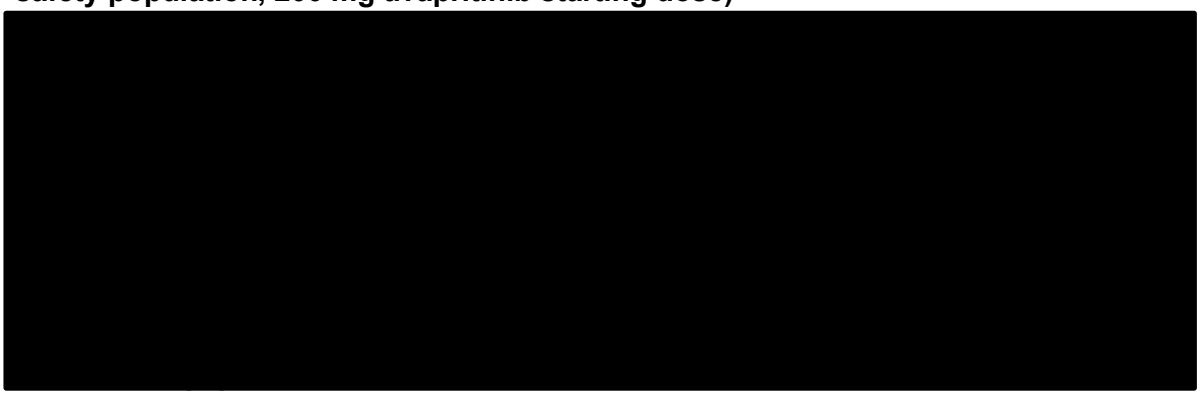
Figure 1. Overall survival by AdvSM subtype (PATHFINDER, safety population, 200 mg avapritinib starting dose)

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematological neoplasm.

Note: The data cut-off for PATHFINDER was 15 September 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

Figure 2. Overall survival by AdvSM subtype (pooled PATHFINDER and EXPLORER, safety population, 200 mg avapritinib starting dose)



Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with an associated haematological neoplasm.

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

When considering prior systemic therapy use in patients enrolled in PATHFINDER (1L and 2L+ cohorts), median OS has not been met in either cohort (Figure 3).[1] As of the data cut-off, in patients who had not received prior systemic therapy, [redacted] of 38 patients were alive and the KM estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[1] In patients who had received prior systemic therapy [redacted] of 67 patients were alive and the KM estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[1]

In pooled PATHFINDER and EXPLORER patients, median OS has not been met in patients who had not received prior systemic therapy, and was [redacted] months (95% CI: [redacted], [redacted]) in patients who had received prior systemic therapy (Figure 4).[2] As of the data cut-off, in patients who had not received prior systemic therapy, [redacted] of 46 patients were alive and the KM estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[1] In patients who had received prior systemic therapy [redacted] of 79 patients were alive and the KM estimate for OS at 24 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[2]

Figure 3. Overall survival by prior systemic therapy (PATHFINDER, safety population, 200 mg avapritinib starting dose)

Note: The data cut-off for PATHFINDER was 15 September 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

Figure 4. Overall survival by prior systemic therapy (pooled PATHFINDER and EXPLORER, safety population, 200 mg avapritinib starting dose)

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.2.3 Progression-free survival

Median PFS in response-evaluable patients (RAC-RE population) who initiated avapritinib at a dose of 200 mg was reached in the 2023 data cut-off for PATHFINDER (Table 5).[1] In both the PATHFINDER and the pooled PATHFINDER and EXPLORER RAC-RE populations, median PFS was [redacted] months.[2,4] In the PATHFINDER population, as of the data cut-off, [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with a median PFS of [redacted]months (95% CI:[redacted], [redacted].[1] In the pooled PATHFINDER and EXPLORER RAC-RE population, as of the data cut-off, [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with a median PFS of [redacted] months (95% CI: [redacted], [redacted].[2]

Table 5. Progression-free survival in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (RAC-RE population)

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	(n=81)	ASM (n=14)	SM-AHN (n=63)	MCL (n=21)	2L+ (n=63)	1L (n=35)	(n=98)
Progression-free survival												
Events, n (%)	[redacted]											
Censors, n (%)	[redacted]											
Kaplan-Meier estimates*												
Median PFS, months (95% CI)	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM (n=13)	SM-AHN (n=53)	MCL (n=15)	2L+ (n=51)	1L (n=30)	(n=81)	ASM (n=14)	SM-AHN (n=63)	MCL (n=21)	2L+ (n=63)	1L (n=35)	(n=98)
12 months (95% CI)	[redacted]											
24 months (95% CI)	[redacted]											
36 months (95% CI)	[redacted]											
48 months (95% CI)	[redacted]						[redacted]					
54 months (95% CI)*	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: 1L, patients who had not received prior systemic therapy; 2L+, patients who had received prior systemic therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, confidence interval; KM, Kaplan-Meier; MCL, mast cell leukaemia; NR, not reported; NE, not evaluable; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with an associated haematological neoplasm.

*The last available follow-up was 54 months.

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

PFS KM curves for PATHFINDER are presented for individual disease subtypes in Figure 5 and for pooled PATHFINDER and EXPLORER in Figure 6.[1,2]

Figure 5. Progression-free survival in patients treated with 200 mg avapritinib starting dose by AdvSM subtype (PATHFINDER RAC-RE population)

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with an associated haematological neoplasm.

Note: The data cut-off for PATHFINDER was 15 September 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.

Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

Figure 6. Progression-free survival in patients treated with 200 mg avapritinib starting dose by AdvSM subtype (pooled PATHFINDER and EXPLORER pooled RAC-RE population)

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with an associated haematological neoplasm.

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

When considering prior systemic therapy use in PATHFINDER patients, as of the data cut-off, in response-evaluable patients who had not received prior systemic therapy, [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with a median PFS of [redacted] months (95% CI: [redacted], [redacted].[1] In response-evaluable patients who received prior systemic therapy, [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with median PFS not yet met (Figure 7).[1]

In pooled PATHFINDER and EXPLORER response-evaluable patients who had not received prior systemic therapy, as of the data cut-off, [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with a median PFS of [redacted] months (95% CI: [redacted], [redacted]).[2] In response-evaluable patients who received prior systemic therapy [redacted] ([redacted]%) patients were censored for analysis and [redacted] ([redacted]%) had died or had disease progression, with a median PFS of [redacted] months (95% CI: [redacted], [redacted] (Figure 8).[2]

Figure 7. Progression-free survival in patients treated with 200 mg avapritinib starting dose by prior systemic therapy (PATHFINDER RAC-RE population)

Abbreviations: RAC-RE, response assessment committee response-evaluable.

Note: The data cut-off for PATHFINDER was 15 September 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

Figure 8. Progression-free survival in patients treated with 200 mg avapritinib starting dose by prior systemic therapy (pooled PATHFINDER and EXPLORER pooled RAC-RE population)

Abbreviations: RAC-RE, response assessment committee response-evaluable.

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.2.4 Measures of mast cell burden

Substantial reductions in measures of mast cell burden, including bone marrow mast cell percentage, serum tryptase levels, *KIT D816V* variant allele fraction (VAF), and spleen volume, were evident in patients in PATHFINDER and in PATHFINDER and EXPLORER (pooled) who initiated avapritinib at a dose of 200 mg (Table 6).[1,2]

Table 6. Changes in mast cell burden in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (safety population)

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM	SM-AHN	MCL	2L+	1L		ASM	SM-AHN	MCL	2L+	1L	
Bone marrow mast cells												
Patients with baseline evaluation, n	[redacted]											
Total clearance, n (%)	[redacted]											
≥50% reduction from baseline, n (%)	[redacted]											
Serum tryptase												
Patients with baseline evaluation, n	[redacted]											
Patients achieving <20 mg/mL, n (%)	[redacted]											

	PATHFINDER						Pooled PATHFINDER and EXPLORER					
	AdvSM subtype			Treatment history		All AdvSM	AdvSM subtype			Treatment history		All AdvSM
	ASM	SM-AHN	MCL	2L+	1L		ASM	SM-AHN	MCL	2L+	1L	
≥50% reduction from baseline, n (%)	[redacted]											
KIT D816V VAF in blood												
Patients with baseline evaluation, n	[redacted]											
Patients with VAF <0.17*, n (%)	[redacted]											
Patients with VAF <1%, n (%)	[redacted]											
≥50% reduction from baseline, n (%)	[redacted]											
Spleen volume												
Patients with baseline evaluation, n	[redacted]											
≥35% reduction, n (%)	[redacted]											

Abbreviations: 1L, first line therapy; 2L+, after 1 prior systemic therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ddPCR, droplet digital polymerase chain reaction; *KIT*, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MCL, mast cell leukaemia; NR, not reported; SM-AHN, systemic mastocytosis with an associated haematological neoplasm; VAF, variant allele fraction.

*The validated reliable threshold of detection using ddPCR for KIT D816V VAF was established as <0.17% for EXPLORER.

Note: The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023 These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER and had received prior systemic therapy. Data are based on the maximum recorded reduction from baseline.

Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.2.5 Duration of treatment

As of the latest data cut-offs, median DoT with avapritinib at a starting dose of 200 mg was [redacted] months in PATHFINDER alone and [redacted] months in the pooled PATHFINDER and EXPLORER analysis (Table 7).[6] In both the PATHFINDER and pooled PATHFINDER and EXPLORER analyses, median treatment duration was longer in 1L patients ([redacted] and [redacted] months, respectively) compared to 2L+ patients ([redacted] and [redacted] months, respectively).[6]

Table 7. Duration of treatment in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (safety population)

Duration of treatment (months)	PATHFINDER			Pooled PATHFINDER and EXPLORER		
	2L+ (n=67)	1L (n=38)	All (N=105)	2L+ (n=79)	1L (n=46)	All (N=125)
Median (range)	[redacted]					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Duration of Treatment is defined as (treatment end date – treatment start date + 1) / 30.4375
Data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.
Source: Avapritinib Systemic Mastocytosis Integrated Summary of Efficacy: Duration on treatment [pooled PATHFINDER and EXPLORER, 2023 data cut-offs][6]

2.1.3 Health-related quality of life

In PATHFINDER, HRQoL outcomes (EORTC-QLQ-C30, AdvSM Symptom Assessment Form [AdvSM-SAF], and Patient Global Impression of Symptom Severity [PGIS]) were collected from baseline to cycle 17 of treatment (68 weeks; cycle length = 28 days), while in EXPLORER, these data were collected in Part 2 of the trial for 12 cycles of treatment (48 weeks; cycle length = 28 days).[1]

The economic model has been updated using the HRQoL data from this most recent data cut-off (Section 2.1.3.1).

2.1.3.1 EORTC QLQ-C30

In patients treated with avapritinib at a starting dose of 200 mg, improved HRQoL was observed via assessment with the EORTC-QLQ-C30.[1] In both the PATHFINDER study alone (Figure 9) and the pooled analysis with PATHFINDER and EXPLORER (Figure 10), a mean increase in EORTC-QLQ-C30 global health status score of [redacted] points (standard deviation [SD]: [redacted]) was observed from baseline to cycle 17 of treatment, indicating a clinically meaningful improvement in overall HRQoL (minimal clinically important difference [MCID] for EORTC-QLQ-C30 of 5–10 points).[1,7] Patients treated with avapritinib on average had improvements in physical, emotional, social, and role-related function (Table 8).[1]

When considering prior systemic therapy use in the PATHFINDER safety population, similar improvements in HRQoL were observed (Table 8).[1] In patients who hadn't received prior systemic therapy, a mean increase in EORTC QLQ-C30 global health status score of

[redacted]points (SD: [redacted]) was observed from baseline to cycle 17 of treatment. In patients who had received prior systemic therapy, a mean increase in EORTC QLQ-C30 global health status score of [redacted] points (SD: [redacted]) was observed from baseline to cycle 17 of treatment.[1] Improvements in EORTC QLQ-C30 were also evident when considering just response-evaluable (RAC-RE) patients who started avapritinib at a dose of 200 mg, regardless of prior systemic therapy use (Table 8).[1]

Figure 9. Change from baseline in EORTC-QLQ-C30 global health status score in patients treated with 200 mg avapritinib starting dose (PATHFINDER safety population)

[redacted]

Abbreviations: CX, cycle X; DX, day X; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; Q1, first quartile; Q3, third quartile; STD, standard deviation.
Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles.
Data were collected up to cycle 12 in EXPLORER.
The data cut-off for this analysis was 15 September 2023.
These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

Figure 10. Change from baseline in EORTC-QLQ-C30 global health status score in patients treated with 200 mg avapritinib starting dose (pooled PATHFINDER and EXPLORER safety population)

[redacted]

Abbreviations: CX, cycle X; DX, day X; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; Q1, first quartile; Q3, third quartile; STD, standard deviation.
Note: One cycle is equal to 28 days. Boxes represent the median and interquartile range, the dashed line and diamonds represent the mean, whiskers represent the 10th and 90th percentiles, and dots represent patients outside of the 10th and 90th percentiles.
Data were collected up to cycle 12 in EXPLORER.
The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023.
These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.
Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

Table 8. Change from baseline to cycle 17 in EORTC-QLQ-C30 domains in patients treated with 200 mg avapritinib starting dose (PATHFINDER)

EORTC-QLQ-C30 domain	Safety population			RAC-RE population		
	All AdvSM	1L	2L+	All AdvSM	1L	2L+
Physical functioning	[redacted]					
Role functioning	[redacted]					
Emotional functioning	[redacted]					
Cognitive functioning	[redacted]					
Social functioning	[redacted]					
Global health status score	[redacted]					

Abbreviations: 1L, patients who had not received prior systemic therapy; 2L+, patients who had received prior systemic therapy; AdvSM, advanced systemic mastocytosis; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; SD, standard deviation.
Note: One cycle is equal to 28 days. Increases in score indicate improvement. Data are from PATHFINDER only as data were collected up to cycle 12 in EXPLORER. The data cut-off for PATHFINDER was 15 September 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER.
Source: PATHFINDER Clinical Summary (2023 data cut-off).[1]

2.1.3.2 AdvSM Symptom Assessment Form

Improvement in HRQoL was also evident in patients treated with avapritinib at a starting dose of 200 mg via the AdvSM Symptom Assessment Form (AdvSM-SAF). In both the PATHFINDER study alone and the pooled analysis with PATHFINDER and EXPLORER, a

decrease in mean total symptom score (TSS) of [redacted] points (SD: [redacted]) was demonstrated from baseline to cycle 18 (72 weeks) of treatment.[1,2]

In both the PATHFINDER analysis and the pooled analysis with PATHFINDER and EXPLORER, patients who had not received prior systemic therapy demonstrated a decrease in mean TSS of [redacted] points (SD: [redacted]) from baseline to cycle 18 (72 weeks).[1] In patients who had received prior systemic therapy, a decrease in mean TSS of [redacted] points (SD: [redacted]) was demonstrated from baseline to cycle 18 (72 weeks).[1,2]

2.1.3.3 Patient Global Impression of Symptom Severity

Patient perception of their symptom severity further suggests improvements in HRQoL in patients treated with 200 mg of avapritinib. Specifically, in PATHFINDER, a mean decrease in PGIS score of [redacted] was observed from baseline to cycle 17 (68 weeks) of treatment.[1] In the pooled analysis of patients from PATHFINDER and EXPLORER, improvement in patient perception of their symptom severity was evidenced by a mean decrease in PGIS score of [redacted] from baseline to cycle 17 (68 weeks) of treatment.[2]

2.1.4 Safety results

As of the most recent data cut-offs for EXPLORER (19 January 2023) and PATHFINDER (15 September 2023), mean treatment duration in patients treated with a 200 mg avapritinib starting dose was [redacted] months (SD: [redacted]) for PATHFINDER alone and [redacted]months (SD: [redacted]) in the pooled analysis of PATHFINDER and EXPLORER.[1,2]

The economic model has been updated with the grade ≥3 AEs observed in ≥2% of patients treated with avapritinib at a starting dose of 200 mg from the latest pooled analysis of PATHFINDER and EXPLORER (Section 2.1.4).[2]

2.1.4.1 Overall summary of adverse events

In the latest data cut-off, the safety profile of avapritinib in patients who initiated treatment at a dose of 200 mg was consistent with the PATHFINDER 2022 data cut-off, with no new safety issues reported (Table 9).[1,2,4] In the pooled analysis, all patients experienced at least one adverse event (AE); [redacted]% of patients experienced a serious AE, [redacted]% of patients experienced an AE of grade 3 severity or worse, and [redacted]% of patients had an AE that led to discontinuation of the study drug.[2] Treatment-related AEs, as assessed by the Investigators, occurred in [redacted]% of patients; [redacted]% of patients experienced serious treatment-related AEs, [redacted]% of patients experienced treatment-related AEs of grade 3 severity or worse, and [redacted]% of patients experienced treatment-related AEs that led to discontinuation of study drug.[2]

As of the data cut-offs, [redacted]% of pooled patients had an AE that led to dose interruption and [redacted]% of patients had an AE that led to dose reduction.[2]

Adverse events of special interest (AESIs) included cognitive effects and intracranial bleeding. As of the data cut-offs, cognitive effects were reported in [redacted] patients ([redacted]%; assessed as related to treatment in [redacted] [[redacted]%] patients).[2] Intracranial bleeding events were reported in [redacted] patients ([redacted]%), all of which were assessed as related to treatment. All patients who experienced intracranial bleeding discontinued treatment.[2]

Table 9. Summary of adverse events in patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (safety population)

Category, n (%)	PATHFINDER (N=105)	Pooled PATHFINDER and EXPLORER (N=125)
Any AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Grade ≥3 AEs	[redacted]	[redacted]
Treatment-related AE	[redacted]	[redacted]
Serious treatment-related AE	[redacted]	[redacted]
Grade ≥3 treatment-related AE	[redacted]	[redacted]
AE leading to discontinuation from study drug	[redacted]	[redacted]
Treatment-related AE leading to discontinuation from study drug	[redacted]	[redacted]
AE leading to dose interruption	[redacted]	[redacted]
AE leading to dose reduction	[redacted]	[redacted]

Abbreviations: AE, adverse event.

The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Sources: PATHFINDER Clinical Summary (2023 data cut-off)[1]; Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.4.2 Common adverse events

A summary of AEs by system organ class and preferred term is provided in Table 10. All AEs that occurred in ≥10% of all patients and all AEs of Grade 3 or higher that occurred in ≥2% of patients are listed.[1,2] In the pooled analysis of PATHFINDER and EXPLORER, fatal AEs occurred in nine patients, including intra-abdominal haemorrhage, necrotising fasciitis, acute kidney injury, acute hepatic failure, endocarditis, sepsis, haemorrhagic shock, Escherichia sepsis, disease progression, pneumonia aspiration, and erosive gastritis.[2] No fatal AEs were related to treatment.[2]

Table 10. Summary of adverse events in ≥10% and Grade ≥3 AEs in ≥2% of patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (safety population)

Category	PATHFINDER (N=105)		Pooled PATHFINDER and EXPLORER (N=125)	
	AEs	Grade ≥3 AEs	AEs	Grade ≥3 AEs
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]

Category	PATHFINDER (N=105)		Pooled PATHFINDER and EXPLORER (N=125)	
	AEs	Grade ≥3 AEs	AEs	Grade ≥3 AEs
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Periorbital oedema	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Category	PATHFINDER (N=105)		Pooled PATHFINDER and EXPLORER (N=125)	
	AEs	Grade ≥3 AEs	AEs	Grade ≥3 AEs
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hyperuricaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hair colour changes	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Note: Adverse events are presented by system organ class (bold) or preferred term if an AE by preferred term occurred in ≥10% of patients. All AEs of Grade 3 or greater that occurred in ≥2% of patients are additionally reported. Grades of severity for AEs are defined by the National Cancer Institute Common Terminology Criteria for Adverse Events. The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.1.4.3 Treatment-related adverse events

A summary of treatment-related AEs by system organ class and preferred term is provided in Table 11. All treatment-related AEs that occurred in ≥10% of all patients and all treatment-related AEs of Grade 3 or higher that occurred in ≥2% of patients are reported.[1,2]

Table 11. Summary of treatment-related adverse events in ≥10% and Grade ≥3 treatment-related AEs in ≥2% of patients treated with 200 mg avapritinib starting dose in PATHFINDER and pooled PATHFINDER and EXPLORER (safety population)

	PATHFINDER (N=105)		Pooled PATHFINDER and EXPLORER (N=125)	
Category	AEs	Grade ≥3 AEs	AEs	Grade ≥3 AEs
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Periorbital oedema	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hair colour changes	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Note: Treatment-related adverse events are presented by system organ class (bold) or preferred term if a treatment-related AE by preferred term occurred in ≥10% of patients. All treatment-related AEs of Grade 3 or greater that occurred in ≥2% of patients are additionally reported. Grades of severity for AEs are defined by the National Cancer Institute Common Terminology Criteria for Adverse Events. The data cut-off for PATHFINDER was 15 September 2023; the data cut-off for EXPLORER was 19 January 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in PATHFINDER and EXPLORER.

Sources: PATHFINDER Clinical Summary (2023 data cut-off);[1] Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

2.2 External control study (Issue 4)

Detailed methods of the ECS study (BLU-285-2405) are provided in the original company submission. The avapritinib cohort consisted of the same pooled safety population presented above, i.e. patients treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).[3]

2.2.1 Distribution of weights

In the construction of IPTW, steps were taken to reduce the variability in propensity scores. Table 12 provides a summary of the distribution of weights used in the IPTW analysis of OS and DoT. The calculated weights were stabilised and truncated at the 1st and 99th percentiles. The mean of the weights is approximately 1 with no extreme weights for all the subgroup analyses of OS and DoT.

Table 12. Truncated stabilised weights for IPTW analyses

Study sample	N	Mean (SD)	Min	Max
Overall survival: 1L 200 mg avapritinib (safety population) vs. 1L midostaurin				
Overall	104	[redacted]	[redacted]	[redacted]
Avapritinib cohort	46	[redacted]	[redacted]	[redacted]
Midostaurin cohort	58	[redacted]	[redacted]	[redacted]
Overall survival: 2L+ 200 mg avapritinib (safety population) vs. 2L+ cladribine				
Overall	108	[redacted]	[redacted]	[redacted]
Avapritinib cohort	79	[redacted]	[redacted]	[redacted]
Cladribine cohort	29	[redacted]	[redacted]	[redacted]
Duration of treatment: 1L 200 mg avapritinib (safety population) vs. 1L midostaurin				
Overall	104	[redacted]	[redacted]	[redacted]
Avapritinib cohort	46	[redacted]	[redacted]	[redacted]
Midostaurin cohort	58	[redacted]	[redacted]	[redacted]
Duration of treatment: 2L+ 200 mg avapritinib (safety population) vs. 2L+ cladribine				
Overall	104	[redacted]	[redacted]	[redacted]
Avapritinib cohort	79	[redacted]	[redacted]	[redacted]
Cladribine cohort	25	[redacted]	[redacted]	[redacted]

Abbreviations: 1L: first line of therapy; 2L+: second or later line of therapy; max: maximum; min: minimum; RAC: Response Assessment Committee; RE: response evaluable; SD: standard deviation.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

Stabilised weights were truncated at the 1st and 99th percentiles.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

2.2.2 Baseline characteristics before and after IPTW

Baseline characteristics before and after IPTW are shown in Table 13, Table 14 and Table 15. The standardised differences between avapritinib and the comparators decreased to <10% for most covariates; however, some differences remained.[3]

Table 13. Summary of baseline characteristics before and after IPTW for overall survival and duration of treatment analyses in 1L avapritinib vs. 1L midostaurin

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]
Number of unique patients	N=46	N=58	-	Effective N=43	Effective N=58	-
Number of lines of therapy	N=46	N=58		Effective N=43	Effective N=58	
Demographic characteristics						
Age (years)[e]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]		[redacted]	[redacted]	
Sex, n (%)						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]		[redacted]	[redacted]	
Region, n (%)						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]		[redacted]	[redacted]	
Medical history						

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]
Performance status						
ECOG[f]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG category, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia,[g] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia,[h] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics						
AdvSM subtype diagnosis,[i] n (%)						
SM-AHN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin involvement						
Any skin involvement, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukocyte count						

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]	Avapritinib[c]	Midostaurin[c]	Standardised difference[d]
≥16 × 10^9/L, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum tryptase[j] (ng/mL)						
≥125 ng/mL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRSF2/ASXL1/RUNX1 mutation panel						
Patients that were tested for at least one mutation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of mutated genes within S/A/R panel, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; max, maximum; MCL, mast cell leukaemia; min, minimum; S/A/R, SRSF2/ASXL1/RUNX1; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; TKI, tyrosine kinase inhibitor.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*Standardised difference greater than 10%.

[a]The index date was the date of initiation of avapritinib for the avapritinib cohort (i.e. patients from the PATHFINDER trial), and the date of initiation of midostaurin therapy received at the study site for the midostaurin cohort (i.e., real-world patients). The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the midostaurin cohort. Unless otherwise specified, characteristics reported are values at or closest to the index date during the baseline period.

[b]Stabilised IPTW weights accounted for age, sex, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 × 10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[c]The safety population from the EXPLORER and PATHFINDER trials was used. The trial and real-world samples were restricted to patients with available ECOG score during any time before to 3 months after the index date. A total of 58 patients were included in the unweighted midostaurin cohort.

[d]For continuous variables, the standardised difference was calculated by dividing the absolute difference in means of avapritinib cohort vs. midostaurin cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with 2 levels, the standardised difference was calculated using the following equation where P1 was the respective proportion of avapritinib cohort, and P2 was the respective proportion of midostaurin cohort: |P1-

P2|/√p(1-p)], where p=(P1+P2)/2. For each variable, a standardised difference greater than 10% was indicative of meaningful imbalance between the two cohort, per Austin and Stuart (2015), and were denoted with "*".

[e]Only the year of birth was collected for the midostaurin cohort. Patients' age was calculated using the mid-point of the birth year as approximate dates of birth.

[f]For the midostaurin cohort, ECOG and Karnofsky scores assessed during any time before to 3 months after the index date were considered. For the lines of therapy for which patients had no ECOG score on record during this period (N=2 lines of therapy), the Karnofsky score closest to the index date in the same period was converted to an ECOG score, if any Karnofsky score was recorded during this period.

[g]For both the avapritinib cohort and the midostaurin cohort, anaemia included reported anaemia and haemoglobin less than 10 g/dL.

[h]For both the avapritinib cohort and the midostaurin cohort, thrombocytopenia included reported thrombocytopenia and platelet count less than 100 x 10^9/L.

[i]The AdvSM subtype was assessed at the last diagnosis evaluation prior to or on the index date. For the avapritinib cohort, the AdvSM subtype diagnoses reported were adjudicated by the response assessment committee.

[j]Observations with missing serum tryptase were imputed as not having serum tryptase greater than or equal to 125 ng/mL.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 14. Summary of baseline characteristics before and after IPTW for overall survival analysis in 2L+ avapritinib vs. 2L+ cladribine

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Number of unique patients	N=79	N=27	-	Effective N=79	Effective N=22	-
Number of lines of therapy	N=79	N=29	-	Effective N=79	Effective N=24	-
Demographic characteristics						
Age (years)[e]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]		[redacted]	[redacted]	
Sex, n (%)						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]		[redacted]	[redacted]	
Region, n (%)						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Europe	[redacted]	[redacted]		[redacted]	[redacted]	
Medical history						
Performance status						
ECOG[f]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG category, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia,[g] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia,[h] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics						
AdvSM subtype diagnosis,[i] n (%)						
SM-AHN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin involvement						
Any skin involvement, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukocyte count						

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
≥16 × 10^9/L, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum tryptase[j] (ng/mL)						
≥125 ng/mL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRSF2/ASXL1/RUNX1 mutation panel						
Patients that were tested for at least one mutation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of mutated genes within S/A/R panel, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy						
Prior systemic therapy						
Patients with prior systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of systemic therapy received, n (%)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatments received, n (%)						
TKI therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Cytotoxic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic or other systemic therapy[k]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agent-level information available	N = 79	N = 29	-	Effective N = 79	Effective N = 24	-
TKI therapy						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytotoxic therapy						
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic						
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon-alpha	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; max, maximum; MCL, mast cell leukaemia; min, minimum; S/A/R, SRSF2/ASXL1/RUNX1; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; TKI, tyrosine kinase inhibitor.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*Standardised difference greater than 10%.

[a]The index date was the date of initiation of avapritinib for the avapritinib cohort (i.e., patients from the PATHFINDER trial), and the date of initiation of each included line of systemic therapy received at the study site for the cladribine cohort (i.e., real-world patients). Patients from the cladribine cohort could contribute multiple lines of therapy. The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the cladribine cohort. Unless otherwise specified, characteristics reported are values at or closest to the index date during the baseline period.

[b]Stabilised IPTW weights accounted for age, sex, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, number of mutated genes within the S/A/R panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[c]The safety population from the EXPLORER and PATHFINDER trials was used. The trial and real-world samples were restricted to patients with available ECOG score during any time before to 3 months after the index date and available duration of treatment endpoint. A total of 29 lines of therapy were contributed by 27 real-world patients in the unweighted cladribine cohort.

[d]For continuous variables, the standardised difference was calculated by dividing the absolute difference in means of avapritinib cohort vs. cladribine cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with 2 levels, the standardised difference was calculated using the following equation where P1 was the respective proportion of avapritinib cohort, and P2 was the respective proportion of cladribine cohort: $|P1-P2|/\sqrt{p(1-p)}$, where $p = (P1+P2)/2$. For each variable, a standardised difference greater than 10% was indicative of meaningful imbalance between the two cohorts per Austin and Stuart (2015), and were denoted with "*"

[e]Only the year of birth was collected for the cladribine cohort. Patients' age was calculated using the mid-point of the birth year as approximate dates of birth.

[f]For the cladribine cohort, ECOG scores assessed during any time before to 3 months after the index date were considered.

[g]For both the avapritinib cohort and the cladribine cohort, anaemia included reported anaemia and haemoglobin less than 10 g/dL.

[h]For both the avapritinib cohort and the cladribine cohort, thrombocytopenia included reported thrombocytopenia and platelet count less than 100×10^9/L.

[i]The AdvSM subtype was assessed at the last diagnosis evaluation prior to or on the index date. For the avapritinib cohort, the AdvSM subtype diagnoses reported were adjudicated by the response assessment committee.

[j]Observations with missing serum tryptase were imputed as not having serum tryptase greater than or equal to 125 ng/mL.

[k]Other systemic therapy included steroids and thalidomide or derivatives.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 15. Summary of baseline characteristics before and after IPTW for duration of treatment analysis in 2L+ avapritinib vs. 2L+ cladribine

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Number of unique patients	N=79	N=24	-	Effective N=79	Effective N=19	-
Number of lines of therapy	N=79	N=25	-	Effective N=79	Effective N=20	-
Demographic characteristics						
Age (years)[e]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]		[redacted]	[redacted]	
Sex, n (%)						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]		[redacted]	[redacted]	
Region, n (%)						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]		[redacted]	[redacted]	
Medical history						
Performance status						
ECOG[f]						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG category, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia,[g] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia,[h] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics						
AdvSM subtype diagnosis,[i] n (%)						
SM-AHN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin involvement						
Any skin involvement, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukocyte count						
≥16 × 10^9/L, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum tryptase[j] (ng/mL)						
≥125 ng/mL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRSF2/ASXL1/RUNX1 mutation panel						
Patients that were tested for at least one mutation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of mutated genes within S/A/R panel, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Prior therapy						
Prior systemic therapy						
Patients with prior systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of systemic therapy received, n (%)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatments received, n (%)						
TKI therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytotoxic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic or other systemic therapy[k]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agent-level information available	N = 79	N = 25	-	Effective N = 79	Effective N = 20	-
TKI therapy						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics[a]	Unweighted sample			IPTW-weighted sample[b]		
	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]	Avapritinib[c]	Cladribine[c]	Standardised Difference[d]
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytotoxic therapy						
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic						
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon-alpha	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; IPTW, inverse probability of treatment weighting; max, maximum; MCL, mast cell leukaemia; min, minimum; S/A/R, SRSF2/ASXL1/RUNX1; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated haematologic neoplasm; TKI, tyrosine kinase inhibitor.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*Standardised difference greater than 10%.

[a]The index date was the date of initiation of avapritinib for the avapritinib cohort (i.e., patients from the PATHFINDER trial), and the date of initiation of each included line of systemic therapy received at the study site for the cladribine cohort (i.e., real-world patients). Patients from the cladribine cohort could contribute multiple lines of therapy. The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the cladribine cohort. Unless otherwise specified, characteristics reported are values at or closest to the index date during the baseline period.

[b]Stabilised IPTW weights accounted for age, sex, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, number of mutated genes within the S/A/R panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[c]The safety population from the EXPLORER and PATHFINDER trials was used. The trial and real-world samples were restricted to patients with available ECOG score during any time before to 3 months after the index date and available duration of treatment endpoint. A total of 29 lines of therapy were contributed by 27 real-world patients in the unweighted cladribine cohort.

[d]For continuous variables, the standardised difference was calculated by dividing the absolute difference in means of avapritinib cohort vs. cladribine cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with 2 levels, the standardised difference was calculated using the following equation where P1 was the respective proportion of avapritinib cohort, and P2 was the respective proportion of cladribine cohort: $|P1-P2|/\sqrt{p(1-p)}$, where $p = (P1+P2)/2$. For each variable, a standardised difference greater than 10% was indicative of meaningful imbalance between the two cohorts per Austin and Stuart (2015), and were denoted with "*"

[e]Only the year of birth was collected for the cladribine cohort. Patients' age was calculated using the mid-point of the birth year as approximate dates of birth.

[f]For the cladribine cohort, ECOG scores assessed during any time before to 3 months after the index date were considered.

[g]For both the avapritinib cohort and the cladribine cohort, anaemia included reported anaemia and haemoglobin less than 10 g/dL.

[h]For both the avapritinib cohort and the cladribine cohort, thrombocytopenia included reported thrombocytopenia and platelet count less than 100×10^9/L.

[i]The AdvSM subtype was assessed at the last diagnosis evaluation prior to or on the index date. For the avapritinib cohort, the AdvSM subtype diagnoses reported were adjudicated by the response assessment committee.

[j]Observations with missing serum tryptase were imputed as not having serum tryptase greater than or equal to 125 ng/mL.

[k]Other systemic therapy included steroids and thalidomide or derivatives.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

2.2.3 Propensity score distributions before and after IPTW weighting

Propensity score density plots that show propensity score overlap before and after IPTW are provided in Appendix A of this addendum. The plots show good overlap of the propensity scores across the OS and DoT analyses in the following subpopulations of patients:

- Those receiving treatment with avapritinib 200mg at 1L in the trials' safety population, and midostaurin ("real-world patients") at 1L.
- Those receiving treatment with avapritinib 200mg at 2L+ in the trials' safety population and cladribine ("real-world patients") at 2L+.

This overlap indicates that patients with similar characteristics are present in both treatment groups, supporting valid causal comparisons.

2.2.4 Results

2.2.4.1 Overall survival

2.2.4.1.1. 1L avapritinib vs. 1L midostaurin

In the unweighted sample of 1L patients, there were [redacted] ([redacted]%) deaths among 46 avapritinib patients and [redacted] ([redacted]%) among 58 midostaurin patients, with a mean follow-up of 32.2 and 26.1 months, respectively.[3] Median OS was not reached (95% CI: NE, NE) for the avapritinib cohort and [redacted] months (95% CI: [redacted], [redacted]) for the midostaurin cohort (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Figure 11).[3]

In the adjusted analysis after IPTW-weighting, with further adjustment for variables with a standardised difference >10% after weighting (see Appendix B of this addendum), avapritinib was still associated with significantly improved OS compared with midostaurin, with an 86% reduction in the risk of death (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Table 16).[3]

Figure 11. Unweighted Kaplan-Meier curves for overall survival for 1L avapritinib vs. 1L midostaurin

Abbreviations: 1L, first line of therapy

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).
*p-value <0.05.
The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.
Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 16. Overall survival for 1L avapritinib vs. 1L midostaurin

Overall survival[a]	Unweighted sample				IPTW-weighted sample[b]			
	Avapritinib	Midostaurin	Estimate (95% CI)	p-value	Avapritinib	Midostaurin	Estimate (95% CI)	p-value
Number of unique patients	N=46	N=58	-	-	Effective N=43	Effective N=58	-	-
Number of lines of therapy	N=46	N=58	-	-	Effective N=43	Effective N=58	-	-
Deaths from unique patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unique patients censored due to avapritinib initiation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unique patients censored due to new primary malignancy after index date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean follow-up (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median overall survival (months) (95% CI)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival rate[e]				**Log-rank p-value[f]**				**Log-rank p-value[f]**
3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival[a]	Unweighted sample				IPTW-weighted sample[b]			
	Avapritinib	Midostaurin	Estimate (95% CI)	p-value	Avapritinib	Midostaurin	Estimate (95% CI)	p-value
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; AdvSM, advanced systemic mastocytosis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable; NR, not reached; S/A/R, SRSF2/ASXL1/RUNX1.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*p-value <0.05.

[a]For the midostaurin cohort, overall survival was defined as the interval of time between initiation of each included line of therapy and death due to any cause. Patients who had not died by the study end date were censored at the date of last contact. For avapritinib patients, overall survival was defined as the time from the first dose of avapritinib to the date of death due to any cause. Patients who were still alive or lost to follow-up were censored at the last known alive date.

[b]Stabilised weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[c]Median overall survival was estimated using the Kaplan-Meier method.

[d]Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference of greater than 10% after weighting, which included sex, region, ECOG score, AdvSM subtype, leukocyte count of 16×10^9 per L or higher, and number of mutated genes within the S/A/R panel, using a doubly robust approach. HR and the corresponding 95% CI and P value were presented. Two-sided P value < 0.05 was considered statistically significant without multiplicity adjustment and was denoted with "*".

[e]Survival rates were obtained using the Nelson-Aalen Estimator.

[f]Overall survival up to each of these timepoints among the unweighted and IPTW-weighted sample were obtained using the Kaplan-Meier method with log-rank test.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

2.2.4.1.2. 2L+ avapritinib vs. 2L+ cladribine

In the unweighted sample of 2L+ patients, there were [redacted] ([redacted]%) deaths among 79 avapritinib patients and [redacted] ([redacted]%) among 27 cladribine patients, with a mean follow-up of 28.5 and 25.1 months, respectively.[3] Median OS was [redacted] months (95% CI: 50.2, NE) for the avapritinib cohort and [redacted] months ([redacted]) for the cladribine cohort (HR: [redacted]; [redacted]95% CI: [redacted], [redacted]; [redacted]) (Figure 12).[3]

In the adjusted analysis after IPTW-weighting, with further adjustment for variables with a standardised difference >10% after weighting (see Appendix B of this addendum), avapritinib was still associated with significantly improved OS compared with cladribine (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Table 17).[3]

Figure 12. Unweighted Kaplan-Meier curves for overall survival for 2L+ avapritinib vs. 2L+ cladribine

Abbreviations: 2L+, second or later line of therapy.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*p-value <0.05.

The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 17. Overall survival for 2L+ avapritinib vs. 2L+ cladribine

Overall survival[a]	Unweighted sample				IPTW-weighted sample[b]			
	Avapritinib	Cladribine	Estimate (95% CI)	p-value	Avapritinib	Cladribine	Estimate (95% CI)	p-value
Number of unique patients	N=79	N=27	-	-	N=79	N=22	-	-
Number of lines of therapy	N=79	N=29	-	-	N=79	N=24	-	-
Deaths from unique patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unique patients censored due to avapritinib initiation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unique patients censored due to new primary malignancy after index date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean follow-up (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median overall survival (months) (95% CI)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival rate[e]				Log-rank p-value[f]				Log-rank p-value[f]

Overall survival[a]	Unweighted sample				IPTW-weighted sample[b]			
	Avapritinib	Cladribine	Estimate (95% CI)	p-value	Avapritinib	Cladribine	Estimate (95% CI)	p-value
3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable; NR, not reached; S/A/R, SRSF2/ASXL1/RUNX1.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*p-value <0.05.

[a]For cladribine cohort, overall survival was defined as the interval of time between initiation of each included line of therapy and death due to any cause. Patients who had not died by the study end date were censored at the date of last contact. For avapritinib patients, overall survival was defined as the time from the first dose of avapritinib to the date of death due to any cause. Patients who were still alive or lost to follow-up were censored at the last known alive date.

[b]Stabilised weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[c]Median overall survival was estimated using the Kaplan-Meier method.

[d]Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference of greater than 10% after weighting, which included sex, region, ECOG score, AdvSM subtype, leukocyte count of 16×10^9 per L or higher, and number of mutated genes within the S/A/R panel, using a doubly robust approach. HR and the corresponding 95% CI and P value were presented. Two-sided P value <0.05 was considered statistically significant without multiplicity adjustment and was denoted with "*".

[e]Survival rates were obtained using the Nelson-Aalen Estimator.

[f]Overall survival up to each of these timepoints among the unweighted and IPTW-weighted sample were obtained using the Kaplan-Meier method with log-rank test.
Source: ECS IPTW 2023 Pooled Safety Population.[3]

2.2.4.2 Duration of treatment

2.2.4.2.1. 1L avapritinib vs. 1L midostaurin

In the unweighted sample of 1L patients, the median duration of treatment was [redacted] months (95% CI: [redacted], [redacted]) in avapritinib patients and [redacted] months (95% CI: [redacted], [redacted]) in midostaurin patients (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Figure 13).[3] In the adjusted analysis after IPTW-weighting, with further adjustment for variables with a standardised difference >10% after weighting (see Appendix B of this addendum), avapritinib was still associated with significantly longer duration of treatment, with a median of [redacted] months (95% CI: [redacted], [redacted]) vs. [redacted] months (95% CI: [redacted], [redacted]) with midostaurin (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Table 18).[3]

Figure 13. Unweighted Kaplan-Meier curves for duration of treatment for 1L avapritinib vs. 1L midostaurin

[redacted]

Abbreviations: 1L, first line of therapy.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*p-value <0.05.

Lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded from the duration of treatment analysis.

The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 18. Duration of treatment for 1L avapritinib vs. 1L midostaurin

Duration of treatment[a]	Unweighted sample[b]				IPTW-weighted sample[c]			
	Avapritinib	Midostaurin	Estimate (95% CI)	p-value	Avapritinib	Midostaurin	Estimate (95% CI)	p-value
Number of unique patients	N=46	N=58	-	-	Effective N=43	Effective N=58	-	-
Number of lines of therapy	N=46	N=58	-	-	Effective N=43	Effective N=58	-	-
Number of discontinued lines of therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored lines of therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median DoT, months (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[e]			[redacted]	[redacted]			[redacted]	[redacted]
Proportion still on treatment[f]				**Log-rank p-value[g]**				**Log-rank p-value[g]**
3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; AdvSM, Advanced systemic mastocytosis; CI, confidence interval; DoT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable; S/A/R, SRSF2/ASXL1/RUNX1.

[a]For the midostaurin cohort, duration of treatment was defined as the interval of time between initiation of a line of systemic treatment (i.e., the index date) and discontinuation of the same line of treatment for any reason. Patients who had not discontinued a given line of therapy by the study end date were censored at the date of last known treatment prescription or medication dose, or the date of last recorded follow-up if the last known treatment prescription or medication dose was unknown. For avapritinib patients, duration of treatment was defined as the interval of time between the first dose date of avapritinib and the last dose date of avapritinib. For patients who had not ended treatment, the date of last dose was the last end of administration date if not missing, and the cutoff date if missing.

[b]Lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded from the duration of treatment analysis.

[c]Stabilised weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[d]Median duration of treatment was estimated using the Kaplan-Meier method.

[e]Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model duration of treatment. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference of greater than 10% after weighting, which included sex, region, ECOG score, AdvSM subtype, leukocyte count of 16×10^9 per L or higher, and number of mutated genes within the S/A/R panel, using a doubly robust approach. HR and the corresponding 95% CI and p-value were presented. Two-sided p-value <0.05 was considered statistically significant without multiplicity adjustment and was denoted with "*".

[f]Proportion of patients with no treatment discontinuation were obtained using the Nelson-Aalen Estimator.

[g]Proportion of patients with no treatment discontinuation at each of these timepoints among the unweighted and IPTW-weighted sample were obtained using the Kaplan-Meier method with log-rank test.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

2.2.4.2.2. 2L+ avapritinib vs. 2L+ cladribine

In the unweighted sample of 2L+ patients, the median duration of treatment was [redacted]months (95% CI: [redacted], [redacted]) in avapritinib patients and [redacted] months (95% CI: [redacted], [redacted]) in cladribine patients (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Figure 14).[3] In the adjusted analysis after IPTW-weighting, with further adjustment for variables with a standardised difference >10% after weighting (see Appendix B of this addendum), avapritinib was still associated with significantly longer duration of treatment, with a median of [redacted] months (95% CI: [redacted], [redacted]) vs. [redacted] months (95% CI: [redacted], [redacted]) with cladribine (HR: [redacted]; 95% CI: [redacted], [redacted]; [redacted]) (Table 19).[3]

Figure 14. Unweighted Kaplan-Meier curves for duration of treatment for 2L+ avapritinib vs. 2L+ cladribine

Abbreviations: 2L+, second or later line of therapy.

The avapritinib cohort consisted of a pooled safety patient population treated with avapritinib at a starting dose of 200 mg from EXPLORER (data cut-off: 19 January 2023) and PATHFINDER (data cut-off: 15 September 2023).

*p-value <0.05.

Lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded from the duration of treatment analysis.

The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

Table 19. Duration of treatment for 2L+ avapritinib vs. 2L+ cladribine

Duration of treatment[a]	Unweighted sample[b]				IPTW-Weighted sample[c]			
	Avapritinib	Cladribine	Estimate (95% CI)	p-value	Avapritinib	Cladribine	Estimate (95% CI)	p-value
Number of unique patients	N=79	N=24	-	-	Effective N=79	Effective N=19	-	-
Number of lines of therapy	N=79	N=25	-	-	Effective N=79	Effective N=20	-	-
Number of discontinued lines of therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored lines of therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median DoT, months (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion still on treatment[f]				**Log-rank p-value[g]**				**Log-rank p-value[g]**
3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; AdvSM, Advanced systemic mastocytosis; CI, confidence interval; DoT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable; S/A/R, SRSF2/ASXL1/RUNX1.

[a]For the cladribine cohort, duration of treatment was defined as the interval of time between initiation of a line of systemic treatment (i.e., the index date) and discontinuation of the same line of treatment for any reason. Patients who had not discontinued a given line of therapy by the study end date were censored at the date of last known treatment prescription or medication dose, or the date of last recorded follow-up if the last known treatment prescription or medication dose was unknown. For avapritinib patients, duration of treatment was defined as the interval of time between the first dose date of avapritinib and the last dose date of avapritinib. For patients who had not ended treatment, the date of last dose was the last end of administration date if not missing, and the cutoff date if missing.

[b]Lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded from the duration of treatment analysis.

[c]Stabilised weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16×10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the SRSF2/ASXL1/RUNX1 (S/A/R) panel. To reduce variability, stabilised weights were capped at the 1st and 99th percentiles.

[d]Median duration of treatment was estimated using the Kaplan-Meier method.

[e]Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model duration of treatment. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardised difference of greater than 10% after weighting, which included sex, region, ECOG score, AdvSM subtype, leukocyte count of 16×10^9 per L or higher, and number of mutated genes within the S/A/R panel, using a doubly robust approach. HR and the corresponding 95% CI and p-value were presented. Two-sided p-value <0.05 was considered statistically significant without multiplicity adjustment and was denoted with "*".

[f]Proportion of patients with no treatment discontinuation were obtained using the Nelson-Aalen Estimator.

[g]Proportion of patients with no treatment discontinuation at each of these timepoints among the unweighted and IPTW-weighted sample were obtained using the Kaplan-Meier method with log-rank test.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

3 Cost-effectiveness analysis

3.1 Company updated base case

3.1.1 Comparators (Issue 1)

The company's updated base case reflects the pooled PATHFINDER 2023 and EXPLORER 2023 data compared with a historic cohort for midostaurin and cladribine, referred to as the external control study (ECS). Midostaurin is considered the main comparator as it is the only therapy licensed for the treatment of AdvSM in the UK and recommended by NICE.[8]

The comparison of avapritinib with cladribine, using data from best available therapy (BAT) as a proxy, presented in the company's original submission has been removed. This amendment to the company base case supersedes Issue 1 raised in the EAG report on excluding midostaurin from the basket of available therapy comparators, as additional evidence is available to inform the comparison of avapritinib with cladribine. Table 20 summarises the comparators included in the economic analysis.

Table 20. Comparators included in the economic analysis.

Comparators included in NICE scope	Population setting	Data source	Justification
Midostaurin	1L	• Base case: data for avapritinib from pooled PATHFINDER 2023 and EXPLORER 2023 compared with midostaurin using data from the ECS, adjusted using IPTW methods. • Scenario: data for avapritinib from PATHFINDER (Sept 2022) compared with midostaurin using data from the ECS, adjusted using IPTW methods.	See section 2.1 and 2.2
Cladribine	2L+	• Base case: data for avapritinib from pooled PATHFINDER 2023 and EXPLORER 2023 compared with cladribine using data from the ECS, adjusted using IPTW methods. • Scenario: data for avapritinib from PATHFINDER (Sept 2022) compared with cladribine using data from the ECS, adjusted using IPTW methods.	See section 2.1 and 2.2

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; ECS, external control study; IPTW, inverse probability of treatment weighting.

3.1.2 Clinical parameters and variables: addressing limitations in the clinical effectiveness evidence (Issues 3)

3.1.2.1 Baseline characteristics

To address Issue 3 on limitation of the effectiveness evidence, the patient population in the economic model has been updated to reflect the latest available data from pooled PATHFINDER (2023) and EXPLORER (2023) (2.1).[2] The previous base case used data from PATHFINDER 2022 alone.[9]

The baseline characteristics for the modelled cohort in terms of age, gender distribution and weight have been updated from PATHFINDER 2022 safety population to the pooled PATHFINDER 2023 and EXPLORER 2023 safety population. The baseline characteristics are similar to those used in the previous company base case, which were deemed representative of patients in UK clinical practice (see CS, section B.3.4.1).[2,9] Table 21 features key patient characteristics as used in the company's updated base case model compared with the baseline characteristics in the original model.

Table 21. Baseline model cohort characteristics in the base case (pooled PATHFINDER 2023 and EXPLORER 2023, 200 mg, safety population compared with PATHFINDER 2022, 200 mg, safety population)

Parameter	Baseline characteristics pooled PATHFINDER 2023 and EXPLORER 2023 (updated base case)		Baseline characteristics PATHFINDER 2022 (original base case)	
	1L patients	2L+ patients	1L patients	2L+ patients
No. of patients	[redacted]	[redacted]	38	67
No. of patients with ASM	[redacted]	[redacted]	7 (18.4%)	14 (20.9%)
No. of patients with SM-AHN	[redacted]	[redacted]	28 (73.7%)	41 (61.2%)
No. of patients with MCL	[redacted]	[redacted]	3 (7.9%)	12 (17.9%)
Male (%)	[redacted]	[redacted]	52.6%	61.19%
Mean age (years)	[redacted]	[redacted]	68.29	66.55
Mean weight (kg)	[redacted]	[redacted]	71.94	72.01
Mean BSA (m^2)	[redacted]	[redacted]	1.83	1.84

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; BSA, body surface area.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs);[2] PATHFINDER Clinical Summary (2022 data cut-off).[9]

3.1.2.2 Clinical parameters and variables

The sources for the clinical parameters have been updated in the company's base case to address Issues 3 and 11 and are summarised in Table 23.

Key efficacy data for avapritinib in the company updated base case comes from the pooled PATHFINDER and EXPLORER trials, where individual patient-level data (IPD) from the 2023 data cut-offs were used to inform the base-case economic analysis.[2] Previously data from PATHFINDER 2022 was used.[9]

Efficacy data for the comparators (current clinical management) comes from indirect comparisons conducted in the updated ECS IPTW analysis (see section 2.2).[3]

3.1.2.3 Allogenic haematopoietic stem cell transplant

Allo-HSCT is not included in the company's base case, it is explored in a scenario analysis. The ORR and CR have been updated in the model with pooled PATHFINDER 2023 and EXPLORER 2023 data.[2]

Table 22 report response rates for the most recent pooled 2023 data cut-off compared to the previous 2022 data cut-off. The latest 2023 data cut-off confirms avapritinib's clinical efficacy remains consistent in comparison to the 2022 data cut-off.

The impact on the cost-effectiveness of avapritinib of updating the ORR and CR using pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off to inform the allo-HSCT scenario is minimal compared to the original scenario presented in the CS ([redacted] in the ICER by [redacted], primarily influenced by general update to pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off).

Table 22. Avapritinib ORR and CR (IWG criteria) from pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off (RAC-RE, 200 mg dose) compared to PATHFINDER 2022 data cut-off (RAC-RE, 200 mg dose)

	Pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off, RAC-RE (updated scenario)				PATHFINDER 2022 and data cut-off, RAC-RE (original scenario)			
Disease subtype	ORR		CR		ORR		CR	
	1L	2L+	1L	2L+	1L	2L+	1L	2L+
ASM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SM-AHN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; ASM, aggressive systemic mastocytosis; CR, complete remission; MCL, mast cell leukemia; ORR, overall response rate; RAC-RE, response assessment committee response evaluable; SM-AH, systemic mastocytosis with associated haematologic neoplasm.

Source: Pooled PATHFINDER and EXPLORER Clinical Summary (2023 data cut-offs).[2]

Table 23:Summary of sources of data used in economic model base case

Clinical parameter	1L vs. midostaurin	2L+ vs. cladribine	EAG issue addressed	Reference in addendum
Baseline characteristics	Pooled PATHFINDER and EXPLORER (2023) Safety 1L, 200 mg dose[2]	Pooled PATHFINDER and EXPLORER (2023) Safety 2L+, 200 mg dose[2]	3	Section 2.1.1.2
OS	ECS analysis: 1L avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]	ECS analysis: 2L+ avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 2L+ cladribine, (IPTW sample)[3]	3 and 6	Section 2.2.4.1
PFS - avapritinib	Pooled PATHFINDER and EXPLORER (2023) RAC-RE 1L, 200 mg dose[2]	Pooled PATHFINDER and EXPLORER (2023) RAC-RE 2L+, 200 mg dose[2]	3 and 7	Section 2.1.2.3
PFS - comparator	1L midostaurin DoT curve used as a proxy for PFS (IPTW sample)[3]	2L+ cladribine DoT curve used as a proxy for PFS (IPTW sample)[3]	No change	Section 2.2.4.2
DoT - avapritinib	ECS analysis: 1L avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]	ECS analysis: 2L+ avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 2L+ cladribine, (IPTW sample)[3]	3 and 8	Section 2.2.4.2
DoT - comparator	ECS analysis: 1L avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]	ECS analysis: 2L+ avapritinib pooled PATHFINDER and EXPLORER (2023) safety population, 200 mg dose vs 2L+ cladribine, (IPTW sample)[3]	3 and 8	Section 2.2.4.2
AEs - avapritinib	Pooled PATHFINDER and EXPLORER (2023) RAC-RE (all lines) 200 mg dose AEs of Grade ≥ 3 reported in >2% of patients (safety population)[2]	Pooled PATHFINDER and EXPLORER (2023) RAC-RE (all lines) 200 mg dose AEs of Grade ≥ 3 reported in >2% of patients (safety population)[2]	3	Section 2.1.4
AEs - comparator	Midostaurin SmPC[10]	Barete et al[11]	N/A	N/A
HRQoL - avapritinib	Pooled PATHFINDER and EXPLORER (2023)[2]	Pooled PATHFINDER and EXPLORER (2023)[2]	11	Section 2.1.3.1
HRQoL – comparator	Pooled PATHFINDER and EXPLORER (2023)[2]	Pooled PATHFINDER and EXPLORER (2023)[2]	11	Section 2.1.3.1

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; AEs, adverse events; DoT, duration of treatment; HRQoL, health-related quality of life; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival; RAC-RE, Response Assessment Committee Response Evaluable population; RWE, real-world evidence.

3.1.3 Adverse events (Issue 3)

The incidence of AEs associated with avapritinib in the model have been updated to reflect the latest pooled PATHFINDER and EXPLORER 2023 analysis (previously PATHFINDER 2022) (Table 24). The analysis included grade 3 and above AEs observed in at least 2% of the patients treated with an avapritinib dose of 200 mg OD. The approach to modelling adverse events for midostaurin and cladribine remains the same as the original company submission, that is based on the data reported in the SmPC for midostaurin and on data reported by Barete et al. for cladribine.[10,11]

Table 24. Cycle probabilities of grade 3+ AEs

	Avapritinib (pooled PATHFINDER 2023 and EXPLORER 2023)[2]	Midostaurin (SmPC)[10]	Cladribine, (Barete et al)[11]
Thrombocytopenia	[redacted]	0.000000	0.014337
Anaemia	[redacted]	0.000000	0.016425
Other haematological disorders	[redacted]	0.002455	0.010608
Gastrointestinal bleed	[redacted]	0.000355	0.000000
Acute myeloid leukaemia	[redacted]	0.000213	0.000000
Sepsis	[redacted]	0.000798	0.000978
Heart failure or shock	[redacted]	0.000070	0.000000
Cardiac arrest	[redacted]	0.000000	0.000000
Cerebrovascular accident, nervous system infections, or encephalopathy	[redacted]	0.000000	0.000000
Haemorrhagic cerebrovascular disorders	[redacted]	0.000000	0.000000
Non-malignant gastrointestinal tract disorders	[redacted]	0.000467	0.000000

	Avapritinib (pooled PATHFINDER 2023 and EXPLORER 2023)[2]	Midostaurin (SmPC)[10]	Cladribine, (Barete et al)[11]
Non-malignant hepatobiliary or pancreatic disorder	[redacted]	0.000701	0.000000
Pneumonia	[redacted]	0.000723	0.000000
Pleural effusion	[redacted]	0.000428	0.000000
Low back pain	[redacted]	0.000000	0.000000
Hypertension	[redacted]	0.000000	0.000000
Syncope or collapse	[redacted]	0.000000	0.000000
Unspecified oedema	[redacted]	0.000213	0.000000
Tendency to fall, senility or other condition affective cognitive functions	[redacted]	0.000000	0.000000
Fever of unknown origin	[redacted]	0.000428	0.000546
Breast disorders	[redacted]	0.000000	0.000000
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	[redacted]	0.000477	0.000000
Sleep disorders	[redacted]	0.000000	0.000000
Other respiratory disorders	[redacted]	0.000262	0.000000
Headache, migraine or cerebrospinal fluid leak	[redacted]	0.000105	0.000000
Peripheral vascular disorders	[redacted]	0.000141	0.000000
Kidney or urinary tract infections	[redacted]	0.000000	0.000000
Skin disorders	[redacted]	0.000141	0.000000
Weight increased	[redacted]	0.000000	0.000000
Appendicitis	[redacted]	0.000000	0.000000
Chronic kidney disease	[redacted]	0.000000	0.000000
Cognitive disorder	[redacted]	0.000000	0.000000
Renal failure	[redacted]	0.000000	0.000000

	Avapritinib (pooled PATHFINDER 2023 and EXPLORER 2023)[2]	Midostaurin (SmPC)[10]	Cladribine, (Barete et al)[11]
Non-malignant, ear, nose, mouth, throat or neck disorders	[redacted]	0.000283	0.000000

Abbreviations: AEs, adverse events; SmPC, Summary of Product Characteristics.

3.1.4 Clinical endpoints and treatment effect (Issue 3, 5, 6, 7 and 8)

The indirect treatment comparison (ITC) was updated using data from pooled PATHFINDER 2023 and EXPLORER 2023 200mg starting dose, addressing EAG Issues 3, 5, 6 and 9.

The ITC used in the economic modelling consists of the following analyses:

- Patients who did not receive prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety population of pooled PATHFINDER 2023 and EXPLORER 2023 compared to 1L patients receiving midostaurin in the real-world cohort.[3]
- Patients who received prior systemic therapy and initiated avapritinib at starting dose of 200 mg in the safety population of pooled PATHFINDER 2023 and EXPLORER 2023 compared to all patients who received cladribine as second line or later (2L+) therapy in the real-world cohort.[3]

Updated pooled 2023 ECS IPTW outcomes for OS and DoT in the safety population are presented further in this section. The parametric fitting of the KM curves was performed identically to that outlined in the company submission (see CS section b.1.2.2.1 for more details).

3.1.4.1 Overall survival - pooled (PATHFINDER 2023 and EXPLORER 2023) IPTW ECS (Issue 3, 5 and 6)

3.1.4.1.1. First-line setting

1L avapritinib

Table 25 features the goodness-of-fit measures for OS. For avapritinib OS (200 mg OD, 1L, safety population), AIC and BIC criteria suggest that, under the separate fitting approach, the Generalised Gamma is the best fitting distribution for OS, followed by the Exponential and the Gompertz functions (see all fitted models for OS in Figure 15).

Table 25. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib OS KM (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
ln Scale	-	[redacted]	[redacted]	-	-	-	-
ln (1/Scale)	-	-	-	[redacted]	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.

Abbreviations: 1L, first line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OD, once daily; OS, overall survival.

Figure 15. Avapritinib 200 mg OS KM curve and parametric distribution fitted (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 1L)

Note: Time is defined in months. The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.

Abbreviations: 1L, first line of therapy; KM, Kaplan-Meier; OS, overall survival.

1L midostaurin

Table 26 feature the goodness-of-fit measures for OS. For midostaurin OS (1L, all AdvSM safety population), AIC and BIC criteria suggest that, under the separate fitting approach, Exponential is the best fitting distribution for OS, followed by the Log-normal and the Gamma functions (see all fitted models for OS in Figure 16).

Table 26. Goodness of fit measures: Objective fitting parametric models to adjusted midostaurin OS KM (safety population, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	-	-	-	-	-	-
ln (1/Scale)	-	-	-	-	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The source of this data is from the ECS analysis of Pooled PATHFINDER 2023 and EXPLORER 2023 (200 mg avapritinib starting dose, safety population, 1L versus 1L midostaurin [IPTW sample]).

Abbreviations: 1L, first line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECS, external control study; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OD, once daily; OS, overall survival.

Figure 16. Midostaurin adjusted OS KM curve and parametric distributions fitted (safety population, 1L)

Note: Time is defined in months. The source of this data is from the ECS analysis of Pooled PATHFINDER 2023 and EXPLORER 2023 (200 mg avapritinib starting dose, safety population, 1L versus 1L midostaurin [IPTW sample]).

Abbreviations: 1L, first line of therapy; ECS, external control study; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OS, overall survival.

3.1.4.1.2. Second-line plus setting

2L+ avapritinib

Table 27 features the goodness-of-fit measures for OS, AIC and BIC criteria suggests that Exponential is the best fitting distribution for OS, followed by the Log-normal and the log-logistic functions (see all fitted models for OS in Figure 17). As Exponential had the best statistical fit, it was chosen for the base case.[12]

Table 27. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib OS KM versus cladribine (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	[redacted]	[redacted]		-	-	-
ln (1/Scale)	-	-	-	[redacted]	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.

Abbreviations: 2L, second or later line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration of treatment; KM, Kaplan-Meier; OD, once daily.

Figure 17. Avapritinib 200 mg OS KM curve and parametric distribution fitted (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 2L+)

Note: Time is defined in months Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023

Abbreviations: 2L, second or later line of therapy; KM, Kaplan-Meier; OS, overall survival.

2L+ cladribine

Table 28 features the goodness-of-fit measures for OS. For cladribine OS (2L+, all AdvSM safety population), AIC and BIC criteria suggest that, under the separate fitting approach, Log-normal is the best fitting distribution for OS, followed by the Log-logistic and the Gompertz functions (see all fitted models for OS Figure 18). Following visual inspection, no issues with this choice where identified.

Table 28. Goodness of fit measures: Objective fitting parametric models to adjusted cladribine OS KM (Safety population, 2L+ setting)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	-	-	-	-	-	-
ln (1/Scale)	-	-	-	-	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: source of this data is from the ECS analysis of pooled PATHFINDER 2023 and EXPLORER 2023 (200 mg avapritinib starting dose, safety population, 2L+ versus 2L+ cladribine [IPTW sample]).

Abbreviations: 2L+, second or later line of therapy; ECS, external control study; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OS, overall survival.

Figure 18. Cladribine OS adjusted KM curve and parametric distributions fitted — safety population, 2L+ setting

Note: Time is defined in months. The source of this data is from the ECS analysis of pooled PATHFINDER 2023 and EXPLORER 2023 (200 mg avapritinib starting dose, safety population, 2L+ versus 2L+ cladribine [IPTW sample]).

Abbreviations: 2L+, second or later line of therapy; ECS, external control study; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OS, overall survival.

3.1.4.2 Duration on treatment - pooled (PATHFINDER 2023 and EXPLORER 2023) IPTW ECS (Issue 3, 5 and 8)

3.1.4.2.1. First line setting

1L avapritinib

Table 29 features the goodness-of-fit measures for DoT. For avapritinib DoT (200 mg OD, 1L, safety population), AIC and BIC criteria suggest that, under the separate fitting approach,

the Exponential is the best fitting distribution for DoT, followed by the Gompertz and the Gamma functions (see all fitted models for DoT in Figure 19).

Table 29. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib DoT KM (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	[redacted]	[redacted]		-	-	-
ln (1/Scale)	-	-	-	[redacted]	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.
Abbreviations: 1L, first line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration of treatment; KM, Kaplan-Meier; OD, once daily.

Figure 19. Avapritinib 200 mg DoT KM curve and parametric distribution fitted (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 1L)

Note: Time is defined in months.The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.
Abbreviations: 1L, first line of therapy; DoT, duration of treatment; KM, Kaplan-Meier.

1L midostaurin

Table 30 features the goodness-of-fit measures for DoT. For midostaurin 1L DoT, AIC and BIC criteria suggest that, under the separate fitting approach, the Log-Normal is the best fitting distribution for DoT, followed by the Exponential and the Generalised Gamma functions (see all fitted models for DoT in Figure 20).

Table 30. Goodness of fit measure: Objective fitting parametric models to adjusted midostaurin DoT KM (safety population, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	-	-	-	-	-	-
ln (1/Scale)	-	-	-	-	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; AIC, Akaike information criterion; BIC, Bayesian information; DoT, duration of treatment; KM, Kaplan-Meier; OD, once daily.

Figure 20. Midostaurin adjusted DoT KM curve and parametric distribution fitted (safety population, 1L)

Note: Time is defined in months.

Abbreviations: 1L, first line of therapy; DoT, duration of treatment; KM, Kaplan-Meier.

3.1.4.2.2. Second line setting

2L+ avapritinib

Table 31 features the goodness-of-fit measures for DoT. For avapritinib DoT (200 mg OD, 2L+, safety population), AIC and BIC criteria suggest that, under the separate fitting approach, the Gompertz is the best fitting distribution for DoT, followed by the Log-logistic and the Weibull functions (see all fitted models for DoT in Figure 21).

Table 31. Goodness of fit measure: Objective fitting parametric models to adjusted avapritinib DoT KM (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	[redacted]	[redacted]		-	-	-
ln (1/Scale)	-	-	-	[redacted]	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-				[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023

Abbreviations: 2L+, second or later line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration of treatment; KM, Kaplan-Meier; OD, once daily.

Figure 21. Avapritinib 200 mg DoT KM curve and parametric distribution fitted (pooled PATHFINDER 2023 and EXPLORER 2023, safety population, 200 mg avapritinib starting dose, 2L+)

[redacted]

Note: Time is defined in months. The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023

Abbreviations: 2L+, second or later line of therapy; DoT, duration of treatment; KM: Kaplan-Meier.

2L+ cladribine

Table 32 features the goodness-of-fit measures for DoT. For cladribine 2L+ DoT, AIC and BIC criteria suggest that, under the separate fitting approach, the Exponential is the best fitting distribution for DoT, followed by the Gamma and the Weibull functions (see all fitted models for DoT in Figure 22).

Table 32. Goodness of fit measure: Objective fitting parametric models to adjusted cladribine DoT KM (safety population, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	-	-	-	-	-	-
ln (1/Scale)	-	-	-	-	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L+, second or later line of therapy; AIC, Akaike information criterion; BIC, Bayesian information; DoT, duration of treatment; KM, Kaplan-Meier; OD, once daily.

Figure 22. Cladribine adjusted DoT KM curve and parametric distribution fitted (safety population, 2L+)

[redacted]

Note: Time is defined in months.

Abbreviations: 2L+, second or later line of therapy; DoT, duration of treatment; KM: Kaplan-Meier.

3.1.4.3 Progression free survival (Issue 3, 5 and 7)

The updated pooled PATHFINDER 2023 and EXPLORER 2023 PFS has reached its median at [redacted] months (1L) and [redacted] months (2L+), addressing EAG concerns regarding immaturity of survival data (Issue 5 and 3).[2] Table 33 and Table 34 report PFS parametric models used in the base case for avapritinib in 1L and 2L+, respectively.

Supplementary material is also provided for the following scenarios:

- Using analysis of PFS compared to midostaurin from 2021 matching-adjusted indirect comparison (MAIC) (see Table 35)
- Applying the OS HR (resulting from the 2023 IPTW ITC) for the comparator (see Table 36).

3.1.4.3.1. Avapritinib: 200 mg OD, RAC-RE population, 1L setting, pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off

For avapritinib PFS (200 mg OD, 1L, RAC-RE population), AIC and BIC criteria suggest that Exponential is the best fitting distribution for PFS, followed by the Log-normal and the Generalised Gamma functions (see all fitted models for PFS in

Figure 23).

Table 33. Goodness of fit measures: Objective fitting parametric models to observed avapritinib PFS KM (pooled PATHFINDER 2023 and EXPLORER 2023, RAC-RE population, 200 mg avapritinib starting dose, 1L)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	-
ln Scale	-	[redacted]	[redacted]		-	-	-
ln (1/Scale)	-	-	-	[redacted]	-	-	-
Scale	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	-	-	-	-	[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.

Abbreviations: 1L, first line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OD, once daily; PFS, progression-free survival; RAC-RE: Response Assessment Committee Response-Evaluable.

Figure 23. Avapritinib 200 mg PFS KM curve and parametric distributions fitted (pooled PATHFINDER 2023 and EXPLORER 2023, RAC-RE population, 200 mg avapritinib starting dose, 1L)

Note: Time is defined in months. The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.
Abbreviations: 1L, first line of therapy; AdvSM: advanced systemic mastocytosis; KM: Kaplan-Meier; PFS: Progression-free survival; RAC-RE: Response Assessment Committee Response-Evaluable.

3.1.4.3.2. Avapritinib 200 mg OD RAC-RE population 2L+, pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off

For avapritinib PFS (200 mg OD, 2L+, RAC-RE population), AIC and BIC criteria suggest that Log-normal is the best fitting distribution for PFS, followed by the Log-logistic and the Weibull functions (see all fitted models for PFS in

Figure 24).

Table 34. Goodness of fit measures: Objective fitting parametric models to observed avapritinib PFS KM (pooled PATHFINDER 2023 and EXPLORER 2023, RAC-RE population, 200 mg avapritinib starting dose, 2L+)

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
ln Scale		[redacted]	[redacted]				
ln (1/Scale)				[redacted]			
Scale		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape					[redacted]	[redacted]	[redacted]
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.
Abbreviations: 2L+, second or later line of therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OD, once daily; PFS, progression-free survival; RAC-RE, Response Assessment Committee Response-Evaluable.

Figure 24. Avapritinib 200 mg PFS KM curve and parametric distributions fitted (pooled PATHFINDER 2023 and EXPLORER 2023, RAC-RE population, 200 mg avapritinib starting dose, 2L+)

Note: Time is defined in months. The data cut-off for this analysis was 2023. These data are from patients who initiated avapritinib at a dose of 200 mg in pooled PATHFINDER 2023 and EXPLORER 2023.

Abbreviations: 2L+, second or later line of therapy; AdvSM, advanced systemic mastocytosis; KM: Kaplan-Meier; PFS, progression-free survival; RAC-RE: Response Assessment Committee Response-Evaluable.

3.1.4.3.3. Progression-free survival in the comparator arm

Figure 25. Midostaurin – survival curves defining health states membership (safety population, as per base case)

Note: This chart reflects only survival extrapolations, according with the distributions selected It does not reflect the impact of including allo-HSCT in the analysis (which is explored in a scenario analysis)
Abbreviations: BAT; best available therapy; DoT, duration of treatment; OS, overall survival; PFS, progression-free survival.

Figure 26. Cladribine survival curves defining health state membership (safety population)

Abbreviations: DoT, duration of treatment; OS, overall survival; PFS, progression-free survival.

Table 35 shows an overview of the PFS HRs sourced from the MAIC;[13] however, results should be interpreted with caution as the MAIC was based on an older data cut-off (pooled PATHFINDER and EXPLORER 2021).[13] Results from using the MAIC HR to derive comparator PFS is explored in a scenario analysis.

Table 35. MAIC ITC results for PFS (2021 data cut)

Avapritinib population	Midostaurin population	HR (95% CI)
Pooled (RAC-RE, overall, n=130)	Pooled (PEP, n=89)	[redacted]
Pooled (RAC-RE, midostaurin-naïve, n=72)	Pooled (PEP, n=89)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; n, total number of patients; PEP, primary efficacy population; RAC-RE, response assessment committee response evaluable.

Source: Blueprint Medicines Data on File.[13]

Table 36 below shows an overview of the OS HRs sourced from the IPTW ITC to inform comparator PFS. This approach is explored in a scenario analysis. Statistical significance was established in the updated results, as a two-sided P-value < 0.05 was considered statistically significant without multiplicity adjustment.

Table 36. Hazard ratios (adjusted HRs for the safety sets, IPTW samples)

IPTW samples	Analysis	Adjusted HR (confidence intervals)	P-values
1L, 200mg OD, avapritinib PATHFINDER (safety population) vs. 1L midostaurin	OS	[redacted]	[redacted]
2L+, 200mg OD, avapritinib PATHFINDER (safety population) vs. 2L+ cladribine	OS	[redacted]	[redacted]

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; OD, once daily; HR, hazard ratio; OS, overall survival.

Source: ECS IPTW 2023 Pooled Safety Population.[3]

3.1.4.4 Measurement and valuation of health effects (Issue 11)

HRQoL data was pooled with PATHFINDER 2023 and EXPLORER 2023 to increase sample size and reduce uncertainty, to address EAG Issue 11.[2] Study protocol and assessments for EORTC QLQ-C30 in PATHFINDER and EXPLORER are outlined in the CS, section B.2.6.1.5.1 and section 2.1.3, in this document. Assessments in EXPLORER were scheduled at day 1 of cycles 1 to 12 (28-day cycle length) and these data were collected in part 2 of the trial for 12 cycles of treatment (i.e. at 48 weeks).[2]

Mapping methodology for EORTC-QLQ-C30 are line with those used in the original CS (see CS, section B.3.5.2).

Please see below the details on numbers of patients providing EORTC QLQ-C30 data at each time point. Using the dimension “AVISIT” or the dimension “ADY/7”.

3.1.4.4.1. Pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off: avapritinib 200mg RAC-RE population, 1L

A total of 262 observations of 33 unique patients were used in the analysis. Table 37 (EORTC QLQ-C30 data) features the data at each time point to inform the mapped utility value associated with PF based on pooled PATHFINDER 2023 and EXPLORER 2023 data-cut (avapritinib 200 mg RAC-RE population, 1L, AdvSM), using the ‘AVISIT’ dimension:

Table 37. Data at each time point to inform the mapped utility value associated with PF, based on pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off, 1L, relying on “AVISIT” dimension.

Timepoint	Nr of patients
Baseline	32
Cycle 1 Day 15	23
Cycle 2 Day 1	25
Cycle 3 Day 1	27
Cycle 5 Day 1	28
Cycle 7 Day 1	21
Cycle 9 Day 1	25
Cycle 11 Day 1	25
Cycle 14 Day 1	18
Cycle 17 Day 1	19

Abbreviations: Nr, number.

Table 38 shows the data collected at each time point (baseline, at end of week 2, week 4 and week 8 and subsequently, every 8 weeks until cycle 17) using the “ADY/7” field (round function used).

Table 38. Detailed breakdown of HRQoL at each time point using "ADY/7" field for 1L patients

Timepoint	Nr patients
Baseline	32
Week 2	23
Week 4	25
Week 8	24
Week 16	20
Week 24	24
Week 32	17
Week 40	17
Week 48	-
Week 56	-

Week 64	10

Abbreviations: Nr, number.

3.1.4.4.2. Pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off - avapritinib 200mg RAC-RE population, 2L+

A total of 447 observations of 60 unique patients were used in the analysis. Note that for two observations the timepoint was blank; however, this observation was still included in the analysis because ADY was available, and it was before progression, using the 'AVISIT' dimension.

Table 39.Data at each time point to inform the mapped utility value associated with PF, based pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off, 2L+, relying on "AVISIT" dimension.

Timepoint	Nr of patients
Baseline	56
Cycle 1 Day 15	42
Cycle 2 Day 1	50
Cycle 3 Day 1	45
Cycle 5 Day 1	41
Cycle 7 Day 1	42
Cycle 9 Day 1	33
Cycle 11 Day 1	31
Cycle 14 Day 1	24
Cycle 17 Day 1	23

Abbreviations: Nr, number.

Table 40 below showcases this detail at each time point (baseline, at end of Week 2, Week 4 and Week 8 and subsequently, every 8 weeks until cycle 17) relying on the "ADY/7" field (round function used).

Table 40. Detailed breakdown of HRQoL at each time point using "ADY/7" field for 2L+ patients

Timepoint	Nr patients
Baseline	56
Week 2	42
Week 4	46
Week 8	38
Week 16	31
Week 24	30
Week 32	23
Week 40	24
Week 48	-
Week 56	1
Week 64	12

Abbreviations: Nr, number.

To map EORTC QLQ-C30 scores to EQ-5D values the utilities were stratified by progression status: First, the progression date of each patient was identified and all the QoL observations prior to that date were used to calculate the average PF utility value for each patient. Finally, the average of each patient values was aggregated in a single score.

While this approach provided reliable results for the utility value associated with the PF health state, it proved futile to define the utility value after progression, since there were too few QoL observation for patients with a PD in the datasets, even when pooling observations from EXPLORER and PATHFINDER to increase the sample size.[2] Therefore, the PD health state utility value (HSUV) was derived following the same methodology outlined in the CS section B.3.5.3.

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

The base-case utility values for PFS health state were derived from pooled PATHFINDER 2023 and EXPLORER 2023 as this was considered the most robust and applicable source of utility data for this population, as data were directly collected from patients with AdvSM.[2] Updated values are similar to the company's original submission, which align with the UK clinical feedback received during the initial submission, see Table 41 for a comparison of the updated HRQoL data with the company original base case.

The values were mapped to EQ-5D-3L which is the preferred method outlined in the NICE reference case.[14]

As stated in CS section B.3.5.3, mapping algorithm requires utility to be stratified by progression status and due to the small sample sizes, this was not possible. Therefore, data from literature was considered robust to address the data gap.

Table 41 summarises the utility values included in the cost-effectiveness base-case. Updated utility values were similar to those used in the previous company base case, which were deemed representative of patients in UK clinical practice. In addition to treatment specific AEs, disutility associated with cladribine administration was included, as described in CS section B.3.5.6 The updated HRQoL data had a minimal impact on the results, with a [redacted] in the ICER.

Table 41. Summary of utility values for cost-effectiveness analysis

State	Updated utility value: mean (standard error)	Original company base case utility value: mean (standard error)	Justification
Progression-free (1L)	[redacted]	[redacted]	Derived from Pooled PATHFINDER 2023 and EXPLORER 2023
Progressed disease (1L)	[redacted]	[redacted]	Derived from Pooled PATHFINDER 2023 and EXPLORER 2023 and TLR

State	Updated utility value: mean (standard error)	Original company base case utility value: mean (standard error)	Justification
Progression-free (2L+)	[redacted]	[redacted]	Derived from Pooled PATHFINDER 2023 and EXPLORER 2023
Progressed disease (2L+)	[redacted]	[redacted]	Derived from Pooled PATHFINDER 2023 and EXPLORER 2023 and TLR
Death	0.000	-	-

Abbreviations: 1L, first line of therapy; 2L+, second or later line of therapy; TLR, targeted literature review.

3.2 Summary of updated base-case analysis inputs and assumptions

3.2.1 Summary of base-case analysis inputs

A summary of the updated base-case inputs included in the model for 1L and 2L+ settings are provided in Table 42 and Table 43.

Probabilistic sensitivity analysis and one-way sensitivity analysis were performed following the same methodology outlined in the original CS (see CS, section B1.5.1 for more information). Results can be found in the company's technical engagement response form.

Table 42. Summary of base case inputs - 1L versus midostaurin

Parameter		Original base case submitted in CS	Updated base case following TE
Population setting		PATHFINDER (September 2022) Safety 1L, 200 mg dose[9]	Pooled PATHFINDER 2023 and EXPLORER 2023. Safety 1L, 200 mg dose[2]
Treatment effect sources			
OS		ECS analysis: 1L avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[15]	Pooled ECS analysis: 1L avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]
PFS	Avapritinib	PATHFINDER (September 2022) RAC-RE 1L, 200 mg dose[9]	Pooled PATHFINDER 2023 and EXPLORER 2023 RAC-RE 1L, 200mg dose[2]
	Midostaurin	ECS analysis: 1L midostaurin unweighted analysis (equivalent to comparator DoT)[15]	Pooled ECS analysis: 1L avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 1L midostaurin (IPTW sample) (equivalent to comparator DoT)[3]
DoT	Avapritinib	RWE, Saunders et al 2022[16]	Pooled ECS analysis: 1L avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]
	Midostaurin	ECS analysis: 1L midostaurin unweighted analysis[15]	Pooled ECS analysis: 1L avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 1L midostaurin (IPTW sample)[3]

Adverse events	Avapritinib	PATHFINDER (September 2022) RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported in >2% of patients by preferred term (safety population)[9]	Pooled PATHFINDER 2023 and EXPLORER 2023 RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported in >2% of patients by preferred term (safety population)[2]
Duration of avapritinib treatment benefit		5 years	7.5 years
Health related quality of life			
Progression free		PATHFINDER September 2022 data cut-off[9]	Pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off[2]
Progressed disease		TLR – Joshi et al, Leunis et al, Mamola et al, Stein et al.[17-20] Application of weighted mean of ratios PD vs. PFS taken from literature.	TLR – Joshi et al, Leunis et al, Mamola et al, Stein et al.[17-20] Application of weighted mean of ratios PD vs. PFS taken from literature.
Extrapolation approach			
Extrapolation approach		Full parametric separate statistical model	Full parametric separate statistical model
OS parametric extrapolation	Avapritinib	Generalised gamma	Generalised gamma
	Midostaurin	Exponential	Exponential
PFS parametric extrapolation	Avapritinib	Generalised gamma	Exponential
DoT parametric extrapolation	Avapritinib	Exponential	Exponential
	Midostaurin	Exponential	Log-Normal

Abbreviations: 1L, first line of therapy; AE, adverse events; CS, company submission; DoT, duration of treatment; ECS, external control study; IPTW, inverse propensity treatment weighting; OS, overall survival, PD, progressed disease; PF, progression free; PFS, progression free survival, RAC-RE, response assessment committee response-evaluable; RWE, real-world evidence; TE, technical engagement; TLR, targeted literature review.

Table 43. Summary of base case inputs – 2L+ versus cladribine

Parameter		Original base case submitted in CS	Updated base case following TE
Population setting		PATHFINDER (September 2022) Safety 2L+, 200 mg dose[9]	Pooled PATHFINDER 2023 and EXPLORER 2023. Safety 2L+, 200 mg dose[2]
Treatment effect sources			
OS		ECS analysis: 2L+ avapritinib PATHFINDER (September 2022) safety population, 200 mg dose vs 1L cladribine (IPTW sample)[21]	Pooled ECS analysis: 2L+ avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 2L+ cladribine (IPTW sample)[3]
PFS	Avapritinib	PATHFINDER (September 2022) RAC-RE 2L+, 200 mg dose[9]	Pooled PATHFINDER 2023 and EXPLORER 2023 RAC-RE 2L+, 200mg dose[2]
	Cladribine	ECS analysis: 2L+ cladribine unweighted analysis (equivalent to comparator DoT)[21]	Pooled ECS analysis: 2L+ avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 2L+ cladribine (IPTW sample) (equivalent to comparator DoT)[3]
DoT	Avapritinib	RWE, Saunders et al 2022[16]	Pooled ECS analysis: 2L+ avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 2L+ cladribine (IPTW sample)[3]
	Cladribine	ECS analysis: 2L+ cladribine unweighted analysis[21]	Pooled ECS analysis: 2L+ avapritinib PATHFINDER 2023 and EXPLORER 2023 (safety population, 200 mg dose vs 2L+ cladribine (IPTW sample)[3]
Adverse events	Avapritinib	PATHFINDER (September 2022) RAC-RE (all lines) 200 mg dose AEs of Grade >3 reported	Pooled PATHFINDER 2023 and EXPLORER 2023 RAC-RE (all lines) 200 mg dose AEs of

		in >2% of patients by preferred term (safety population)[9]	Grade >3 reported in >2% of patients by preferred term (safety population)[2]
Duration of avapritinib treatment benefit		5 years	7.5 years
Health related quality of life			
Progression free		PATHFINDER September 2022 data cut-off[9]	Pooled PATHFINDER 2023 and EXPLORER 2023 data cut-off[2]
Progressed disease		TLR – Joshi et al, Leunis et al, Mamola et al, Stein et al. [17,18] [19,20] Application of weighted mean of ratios PD vs. PFS taken from literature.	TLR – Joshi et al, Leunis et al, Mamola et al, Stein et al. [17,18] [19,20] Application of weighted mean of ratios PD vs. PFS taken from literature.
Extrapolation approach			
Extrapolation approach		Full parametric separate statistical model	Full parametric separate statistical model
OS parametric extrapolation	Avapritinib	Generalised gamma	Exponential
	Cladribine	Exponential	Log-normal
PFS parametric extrapolation	Avapritinib	Generalised gamma	Log-normal
DoT parametric extrapolation	Avapritinib	Exponential	Gompertz
	Cladribine	Exponential	Exponential

Abbreviations: 2L+, second or later line of therapy; AE, adverse events; CS, company submission; DoT, duration of treatment; ECS, external control study; IPTW, inverse propensity treatment weighting; OS, overall survival, PD, progressed disease; PF, progression free; PFS, progression free survival, RAC-RE, response assessment committee response-evaluable; RWE, real-world evidence; TE, technical engagement; TLR, targeted literature review.

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5 Appendices

Appendix A and Appendix B of this addendum are embedded below and provided as Excel files in the reference pack accompanying this addendum.


Appendix A


Appendix B

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

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. 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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **14 June 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Clinical expert statement

NICE National Institute for Health and Care Excellence

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.

Part 1: Treating advanced systemic mastocytosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Andrew Whyte
2. Name of organisation	University Hospitals Plymouth NHS Trust Nominated by: - Royal College of Physicians, and - British Society for Allergy and Clinical Immunology
3. Job title or position	Consultant Allergist and Immunologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced systemic mastocytosis? ☐ A specialist in the clinical evidence base for advanced systemic mastocytosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

Clinical expert statement

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for advanced systemic mastocytosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Mastocytosis is an extremely heterogenous disease and the main aim of treatment can differ between individuals. 1. For many patients the main goal is reduction in symptom burden and corresponding increase in health-related quality of life. Mastocytosis can be extremely symptomatic, with the worst symptoms reported by patients being very heterogeneous but most commonly including fatigue, skin problems (e.g. itching, flushing, rashes), gastrointestinal symptoms like frequent/severe diarrhoea, and neurocognitive symptoms (e.g. “brain fog”, headaches). 2. The other aim of treatment can be amelioration of complications related to organomegaly or organ dysfunction, measured with histopathological response criteria, which can correlate with better prognosis with its associated benefits to mental health. Ultimately the main aim will differ slightly between patients and the goal will be identified through shared decision making.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Mastocytosis can present in a variety of ways and different patients are affected in different ways so a shared decision-making framework is essential in deciding what the most significant improvement would be for an individual patient. This may be subjective, but from an objective standpoint the mIWG-MRT-ECNM criteria provide a good framework for assessment of treatment response as they include a measure of symptomatic improvement which is very valuable.

10. In your view, is there an unmet need for patients and healthcare professionals in advanced systemic mastocytosis?	I think significant currently unmet needs are (a) the need for additional targeted treatments other than midostaurin for people who are unsuitable for, intolerant of, or unresponsive to midostaurin, and (b) to define the molecular and histopathological characteristics that can separate the associated haematological neoplasm (AHN) in therapeutically useful categories. The SM component can respond to midostaurin, often very well to avapritinib, but it's often the AHN that progresses and determines prognosis, so understanding the factors that feed into who progresses and when be of great benefit.
11. How is advanced systemic mastocytosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are several aspects to the treatment of AdvSM. The approach is broadly consistent between clinicians and centres; there are no formal UK guidelines although a working group has now been formed for this purpose. Most patients will require symptomatic treatment (e.g. with H1 and H2 antihistamines, leukotriene antagonists, sodium cromoglicate, adrenaline etc) and many will require treatment of complications (e.g. bisphosphonates, proton pump inhibitors etc), although these are not disease-modifying. Tyrosine kinase inhibitors would be first-line therapy in the NHS for the majority of patients. In those who either are not suitable for (e.g. cardiac disease), do not respond to, or are intolerant of midostaurin (or other TKIs), a variety of alternative (unlicensed) treatments may be used including cladribine (first-line or second-line, especially for rapid reduction in disease burden) and imatinib (in patients with wildtype CKIT, although this is a very small minority). Interferon alpha is very rarely used since the advent of TKIs. Haematopoietic stem cell transplant (HSCT) is the only therapy that may be curative, and it may be appropriate for some patients (especially

	younger patients with more aggressive disease and fewer comorbidities). The most important predictor of good outcome with HSCT is minimal disease at time of transplant. Midostaurin can induce good partial response (PR) but very rarely complete response (with or without resolution of haematological parameters; CR and CRh). In contrast the evidence suggests that avapritinib induces deep and durable responses (CR and CRh) which would (a) potentially make more patients eligible for HSCT, and (b) improve outcome following HSCT.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It would not affect resource use compared to current practice. It would be prescribed and monitored in secondary care in much the same way as midostaurin.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The evidence suggests that the overall response rate is much better for avapritinib than midostaurin or imatinib, and clinical experience supports this view. Midostaurin can induce good PR but rarely CR or CRh as avapritinib can. Avapritinib seems to control pure aggressive systemic mastocytosis (ASM) and mast cell leukaemia (MCL) very well, and in patients with SM-AHN the SM disease component responds well and the AHN is the main reason for progression (approximately 20-25% of patients will progress; >90% of which will be the AHN rather than the SM). The D816V CKIT variant can be present in non-mast cells (e.g.

	monocytes and eosinophils in CMML) and these can also respond to avapritinib. With better SM disease control more patients may be eligible for a curative treatment (HSCT).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some patients may not be suitable for treatment with avapritinib, including patients whose platelet count is <50/uL, those with a history of intracranial haemorrhage, long QTc interval, or those with significant cardiac failure. Some of these would not be suitable for midostaurin either.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There would be no significant difference to midostaurin.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stopping criteria would be in line with the product license.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily	I think the QALY calculation covers the important health-related benefits. With regard to ease of use a minor point is that the daily dosing of avapritinib may be slightly more preferable than the twice-daily dosing of midostaurin.

administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Avapritinib does seem to be a step-change in management of AdvSM in that it seems to provide deeper and more durable responses for the AdvSM such that the AHN often has a greater impact in determining prognosis. The depth of response to avapritinib (including CR and CRh) is also very important in optimising patients for consideration of HSCT where the major prognostic factor for outcome is minimisation of disease at time of transplant.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Avapritinib is usually well tolerated and few patients have significant adverse effects. The most common adverse effects in my experience are periorbital and peripheral oedema which can affect quality of life but can be manageable with dose reduction, interruption, and symptomatic treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	I think the trials do reflect UK practice in that there is a mix of treatment-naïve patients (who would receive avapritinib as the first targeted therapy) and those with previous systemic therapy (often midostaurin, sometimes cladribine or occasionally imatinib). The outcomes are those which are already considered important in UK practice.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Data was presented at the European Hematology Association 2024 which shows evidence through September 2023, demonstrating persistence of benefit.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA728]?	I'm not aware of any major trials of alternative treatments other than inclusion in trials of avapritinib and other newer treatments, beyond those already included in the appraisal.
23. How do data on real-world experience compare with the trial data?	From my own experience and discussion with colleagues the real-world experience matches the trial data and is consistent across global regions.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	I don't foresee any issues related to equality.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines The main comparator for avapritinib is midostaurin as a first-line (1L) treatment option. Best available therapy (BAT) is the	The clinical approach to AdvSM involves (a) clinicopathological assessment and subclassification of the disease into ASM, SM-AHN (approximately 70% of AdvSM), or MCL; (b) assessment of patient fitness/suitability for treatment; (c) in patients with SM-AHN determination of which component of the disease needs more immediate treatment; (d) decision regarding first-line treatment; and (e) consideration of alternative treatments if required. Assessment of suitability for treatments includes investigations (e.g. platelet count, echocardiogram, ECG, and others), the results of which may mean that a particular treatment is unsuitable. Patients with SM-AHN require careful assessment to determine if the clinical and pathological abnormalities are due to the SM or the AHN, as this would then help target treatment to the predominant condition. AHN-dominant patients may then receive a variety of treatments and if helpful the SM may then become dominant and treatment options may change. In patients with ASM, MCL, and SM-dominant disease TKIs would be the first-line treatment in the large majority of patients, and midostaurin (or clinical trial) would currently be the usual choice. Occasionally

Clinical expert statement

comparator at second or subsequent lines (2L+) of therapy. However, this comprises a range of off-label therapies including imatinib, interferon alpha and other off-label therapies not included in the NICE scope. It also includes midostaurin, which is typically given at first line. Clarity regarding what therapies are given in the NHS after midostaurin and the proportion of patients receiving midostaurin as second or subsequent line therapy would be helpful.	patients with sufficient SM-related disease to make TKIs unsuitable (e.g. platelet count <50) a course of cladribine can be helpful first-line to debulk the SM as a bridge to TKIs. Finally if midostaurin is not tolerated or the patient achieves a PR and plateaus reassessment to determine if the SM or the AHN is responsible for the persistent abnormalities is required, and if it is the SM component a switch in treatment would be considered, and an alternative TKI would be very helpful in this circumstance; currently a clinical trial, or cladribine would be the main alternatives with a range of others in BAT. Similarly in patients who received cladribine or other treatments first-line a switch to midostaurin, clinical trial, imatinib (if wildtype CKIT), or occasionally other treatments would constitute BAT. Conversely if the AHN component is progressing treatment of that would be required. Finally, a HSCT would be an option that may treat both the SM and the AHN, although not all patients are suitable for this. The use of a range of comparators at second line is therefore appropriate, in my view.

Issue 2: Separation of the population by treatment line The population in this appraisal has been separated according to treatment line, however NICE's recommendation for midostaurin is not restricted to 1L. Therefore, the EAG consider that treatment comparisons may not reflect the likely treatment pathway for advanced mastocytosis in the UK. Clarity around the likely treatment pathway in the UK would be helpful.	As described in Issue 1 the availability of more than one TKI (especially one with the effectiveness of avapritinib) would be very helpful as part of the treatment pathway of patients with AdvSM. My view is that avapritinib would be of benefit both as first-line and second-line treatment, and discussion with colleagues indicates that they would use it in a broadly similar way. In older patients with more comorbidities midostaurin may be appropriate first-line. It can induce good PRs, and if other aspects of the patient's health are likely to be more significant than the SM in determining prognosis the midostaurin may control it sufficiently. If they reach a plateau of response a switch to avapritinib (or clinical trial if they meet the eligibility criteria) might be preferred, or if necessary (e.g. contraindications to avapritinib/TKIs) the range of current alternative treatments. In patients with more aggressive disease, fewer comorbidities and those who may be suitable for HSCT avapritinib would be better as it seems to produce deeper and more durable responses than midostaurin. Such responses may allow more patients to be eligible for a potentially curative HSCT (in which minimisation of disease burden at time of transplant is the major predictor of better outcome). If the patient has a response plateau or progression, is intolerant of avapritinib, or develops contraindications a switch to midostaurin might be considered, or the range of other BAT depending on individual patient circumstances. There are other factors (such as molecular mutation status) which may help determine which TKI might be more suitable for different patients.
Issue 3: Limitations of the	

effectiveness evidence There are no comparative studies of avapritinib. The effectiveness evidence comes from two single arm studies, of which one is completed and one is still ongoing and results are immature**.**	
Issue 4: Limitations of the indirect treatment comparisons There are uncertainties in the indirect comparison owing to limited reporting and inappropriate adjustment for baseline characteristics.	
Issue 5: Lack of consistency in the	

source of evidence used to inform the different survival parameters in the model There is a lack of consistency in the sources of data used to inform the different survival parameters in the model.	
Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations The OS data used in the company's base case analysis from PATHFINDER at the September 2022 data cut-off is immature, with median OS not reached in either population. The immature OS data is	

extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which lead to very different long-term survival outcomes.	
Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS PFS was not available from the external control study to enable an inverse probability of treatment weighting (IPTW) comparison with PATHFINDER. Therefore, the company uses the comparator's TOT curve as a proxy for the comparator's	

Clinical expert statement

PFS curve, but not for avapritinib. As a consequence, patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression, whereas avapritinib is modelled to receive QALY gains for patients who interrupt treatment before progression, with no treatment costs after discontinuation.	
Issue 8: Source of evidence used to inform time on treatment in the model TOT for avapritinib is sourced from a small cohort of 13 patients	My view, from experience and speaking with colleagues, is that patients remain on avapritinib for at least 3 years with persistence of good response. The expectation is that 5-7 years is a reasonable estimate for most patients.

Clinical expert statement

treated with avapritinib in the UK as part of the Compassionate Use Program. The EAG considers the choice of TOT curve for avapritinib as a major limitation of the company's base case.	
Issue 9: Uncertain duration of treatment benefit for avapritinib The duration of treatment benefit for avapritinib is uncertain. Insight into how long people may be expected to stay on avapritinib would be helpful, as this would allow for better estimation of its treatment benefit.	The avapritinib response rate seems persistent to 3 years so it seems likely that many patients would receive it for at least 5-7 years, based on current evidence and discussion with colleagues. Whether the response of the SM component to avapritinib deepens with time (e.g. developing from PR to CR or CRh) or progress over longer than 5 years isn't certain on the available evidence. Some patients may become eligible for HSCT as a curative option sooner, who wouldn't have otherwise been suitable for this treatment with midostaurin, and notably the majority of progression in SM-AHN relates to the AHN rather than the SM component but nevertheless this may affect TOT estimates.

Issue 10: Exclusion of subsequent therapy The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment is not considered in the company's base case analysis in the 1L or 2L+ populations. Information on treatments used post-avapritinib discontinuation and numbers of people eligible to receive allogenic haematopoietic stem cell transplant would be helpful, along with information regarding post-progression survival outcomes for people with advanced	In patients whose SM insufficiently responds to, are intolerant of, or develop contraindications to first-line avapritinib a switch to midostaurin would be considered. Similarly those receiving midostaurin first-line would switch to avapritinib, and if both TKIs are unsuitable cladribine would be considered. At each stage if the SM component is insufficiently responsive to treatment the patient would be reassessed to ensure that the clinicopathological features are not due to the AHN, and if not a clinical trial or palliation may be considered. If the AHN is the primary problem then a range of therapies would be used to address the relevant AHN (e.g. MDS, MPN, AML etc). Discussion with colleagues suggests that approximately 20-25% of patients with AdvSM on avapritinib will progress, of which the large majority would have progression of the AHN component. Among these patients between 30-50% may be suitable for HSCT.

Clinical expert statement

systemic mastocytosis.	
Issue 11: Uncertainty in the PF and PD health state utility values The utility values for the progression-free (PF) and progressive disease (PD) health states are uncertain. The utility data is based on the PATHFINDER September 2022 data cut-off (i.e., not the latest September 2023 data cut-off) where there are a limited number of observations at each time point used to inform the mapped utility value associated with PF in the 1L and 2L+ populations.	My experience is that patients with progression-free disease (assuming this means symptoms rather than haematological response – PR, CR etc) tend to have good quality of life with fewer symptoms and a lifestyle closer to their baseline state. Prior to treatment the exact clinical presentation is very heterogenous, but patients often describe debilitating fatigue, neurocognitive, cutaneous, gastrointestinal, abdominal, and musculoskeletal symptoms. In severe cases this can result in loss of hobbies, employment, social interaction, along with the mental health aspect of having a chronic and life-limiting disease. With disease-modifying treatment with TKIs patients with PF disease often have a marked reduction in symptoms and are able to return to a more normal level of function, quality of life, mental health, able to go on holidays etc. As disease progresses an early sign is often fatigue followed by a return of the initial symptoms resulting in the loss of quality of life for a second time. This is frequently evident before the haematological parameters worsen, but the rapidity of progression is very individual and symptoms/impact are heterogenous.

Information about how quality of life would differ between people who are progression-free and those who have progressive disease would be helpful.	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

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. 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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **14 June 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Clinical expert statement

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.

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced systemic mastocytosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Jonathan Lambert
2. Name of organisation	University College Hospitals London NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced systemic mastocytosis? ☐ A specialist in the clinical evidence base for advanced systemic mastocytosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for advanced systemic mastocytosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1. Reduce SM-associated disease burden in order to reverse organ damage 2. Extend overall survival 3. Improve quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in SM-associated disease burden (as measured by degree of organ [primarily bone marrow] infiltration, serum tryptase levels, mutant KIT allele burden) and reversal of organ dysfunction (reduction in pleural effusions/ascites, improvement in liver function and blood counts)
10. In your view, is there an unmet need for patients and healthcare professionals in advanced systemic mastocytosis?	Yes, undoubtedly
11. How is advanced systemic mastocytosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• There are currently no formal UK clinical guidelines for managing advanced SM (AdvSM) – practice is based on expert opinion – but British Society for Haematology (BSH) guidelines are in progress. • Pathway of care is not formally defined but since these are extremely rare, complex and life-threatening disorders, most patients are referred to specialist tertiary centres for care, so most UK patients will be treated by a limited number of MPN/mastocytosis specialists. Within this small community of UK

• What impact would the technology have on the current pathway of care?	MPN/mastocytosis specialists, there is close collaboration and generally good agreement on management approach to patients with advanced SM. • Currently, delivering optimal care for people with AdvSM can be challenging, owing to a number of factors: 1. the extreme rarity of the condition (probably the rarest of all the haematological cancers I manage); 2. marked heterogeneity in clinical and molecular characteristics of the disease; 3. the fact that patients are often quite debilitated by their SM-associated symptoms and organ damage by the time of presentation (and may deteriorate quickly after diagnosis), constraining therapeutic options and eligibility for clinical trials; 4. patients often have to travel considerable distances for treatment (they are typically managed in tertiary referral units which may be distant from their own home) – and they can require frequent visits whilst disease is active e.g. for drainage of pleural effusions/ascites, sometimes several times a week; 5. the limited efficacy of the therapies currently available as standard-of-care in NHS clinical practice.

	• Introducing avapritinib as a treatment option would, I believe, significantly improve pathway of care for patients with AdvSM – my experience when using it via the Compassionate Access route was that disease burden fell much quicker (and patient wellbeing improved more rapidly) compared to existing therapies, allowing them to be discharged from inpatient care sooner, and to return to independent daily life. Adoption of avapritinib into routine practice may also allow a shared care model (between regional tertiary and local secondary care hospitals) to be developed so that once patient's clinical condition has improved, some of their care can be delivered locally, reducing the burden of travel to tertiary referral centre.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• Current NHS therapy for AdvSM primarily comprises oral midostaurin (alternatively, cladribine, other cytoreductive agents or clinical trials where available), generally delivered as outpatient in tertiary referral centres (although some patients need inpatient care intermittently due to SM-related organ damage). Avapritinib is also an oral agent and would delivered in the same outpatient setting as midostaurin, so resource use would be similar to midostaurin, and less compared with cladribine (cladribine needs to be administered IV or SC, and is much more immunosuppressive than avapritinib/ midostaurin, resulting in a higher risk of needing admission for treatment of infections) or trials. My experience has been that patients receiving avapritinib tend to improve quicker than those on midostaurin (e.g. SM-related effusions/ascites resolve quicker meaning fewer drainage procedures), so its use may lead to reduced

Clinical expert statement

	requirement for inpatient and daycare facilities. • Avapritinib would only be used in secondary/tertiary care • No additional investment is required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Yes I expect Avapritinib to extend length of life compared to midostaurin. Whilst there are no RCTs comparing the 2 drugs, a large, multi-centre retrospective study comparing Avapritinib with best available therapy (BAT; 50% midostaurin, 25% cladribine) has been performed (Reiter et al, Leukemia 36, 2108–2120, 2022). Patients who received Avapritinib, whether 1st or 2nd line, had a statistically significant longer overall survival (OS) compared with those who received BAT: - Median OS for 1st line Avapritinib vs BAT was 49 vs 27 months, HR 0.40 (95% CI: 0.22, 0.74); p = 0.003 - Median OS for 2nd line Avapritinib vs BAT was not reached vs 17 months, HR 0.37 (95% CI: 0.18, 0.75); p = 0.006. [*Update 15/6/24 following today's oral abstract presentation at European Society for Hematology Annual Scientific meeting by Dr Andreas Reiter, based on Pathfinder study with data cut-off of September 2023:* - with median follow-up of 38 months, median duration of response, PFS and OS were not reached for cohort overall; - for aggressive SM subgroup, OS was 93% at 36 months; - for AdvSM-AHN subgroup, OS was 70% at 36 months; - for mast cell leukaemia subgroup, OS was 72% at 36 months.

	All these OS estimates are much better than historical reports, and represent, in view, a step change in outcomes.] • Yes I expect Avapritinib to increase health-related QOL more compared to current care. Both Avapritinib and Midostaurin are associated with significant improvements in QOL (Gotlib et al, N Engl J Med 2016;374:2530-2541; and Gotlib et al, Nat Med 2021; 27(12): 2192–2199) and there are no direct comparisons between the two agents in terms of QOL. However Reiter et al (Leukemia 2022) observed in the retrospective study cited above that compared with BAT, Avapritinib therapy was associated with a significant longer duration of response to therapy, implying that the effect on QOL will be more prolonged. In addition, my clinical experience, having treated AdvSM patients with both agents, has been that those receiving midostaurin report more residual AdvSM symptoms (especially fatigue) and more treatment-associated toxicity, especially GI toxicity, compared with those receiving Avapritinib, meaning that, anecdotally, midostaurin therapy seems to be associated with poorer patient QOL (and more time spent attending hospital appointments) than does avapritinib therapy.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• No – Avapritinib therapy is only being considered here for patients with AdvSM, which is a very small patient cohort, and the available data indicates that all subgroups of AdvSM benefit from Avapritinib therapy

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	• I anticipate avapritinib will be similar in terms of ease of use compared with midostaurin. Both are oral agents, usually prescribed for outpatient therapy from specialist centres. Compared with cladribine (used relatively rarely) for AdvSM, avapritinib will be easier to deliver as cladribine need to be given IV or SC, usually in a chemotherapy daycare setting over 5 days, and cladribine has higher acute toxicity rates (primarily low blood counts and infections) than avapritinib.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Patients would need to fulfil the criteria for AdvSM to start treatment with avapritinib. Patients' response to the drug would need to be evaluated at specific time points and the drug stopped for patients who fail to respond, or who lose response after an initial response. Time points for response assessment and criteria for stopping the drug in the event of inadequate response remain to be defined. These criteria would be based on parameters already tested for in routine practice (clinical findings, blood counts, BM biopsies, serum tryptase levels). • Current care to evaluate response in patients with AdvSM involves clinical assessment, periodic routine blood tests (FBC, renal, liver function, tryptase), and in some cases abdominal imaging. I expect this to remain unchanged if avapritinib becomes a treatment option for these patients.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or	• My experience has been that patients receiving avapritinib tend recover their independence (in terms of activities of daily living) quicker than those receiving midostaurin, meaning they are less dependent on carers, able to return to work, less likely to need inpatient care etc. I'm not sure if these aspects are fully captured in the QALY calculation.

have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Yes – AdvSM is an unmet clinical need and my view (and that of other AdvSM expert clinicians I have spoken to) is that avapritinib is likely to represent a step change for the treatment of AdvSM. The trial data for avapritinib indicates that it is a disease modifying agent, in terms of dramatically suppressing the underlying pathological process (the KIT D816V+ve malignant clone in AdvSM), reducing disease bulk (as measured by malignant mast cells present in the bone marrow and serum tryptase levels) and markedly extending patient overall survival. My clinical experience mirrors the trial data. Patients I've treated with avapritinib have generally returned to near-normal daily life (in terms of activities of daily living, return to employment, caregiving activities) and once they have stabilised on therapy, generally need less frequent ad-hoc medical reviews than patients on other treatments. They remain on treatment several years after starting avapritinib despite having had serious manifestations of the disease at diagnosis (now largely resolved), with good quality of life. By contrast, existing therapies for advSM (primarily midostaurin and cladribine) provide relatively modest improvements to clinical wellbeing and extension of life expectancy. AdvSM patients taking these therapies very rarely return to a normal or near-normal lifestyle, due to residual AdvSM symptoms, side effects of treatment (including

	GI toxicities and cytopenias), and the need for frequent hospital attendance to deal with troublesome symptoms. .
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• For most patients, the commonest side effects of avapritinib (low blood counts, fatigue, hair colour changes, peripheral oedema, diarrhoea) are generally mild and well tolerated, and can be ameliorated with dose reductions, with affecting their QOL.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Yes international trials of avapritinib do reflect UK practice - UK patients participated in the key Pathfinder and Explorer studies (Gotlib et al, Nature Medicine 2021, 27:2192–2199; and DeAngelo et al, Nature Medicine 2021, 27:2183–2191). Further, in the UK clinical setting, patients with AdvSM are treated by a relatively small number of SM expert clinicians who adhere closely to the internationally-accepted diagnostic criteria for AdvSM used in the trials, so I expect future patients treated with avapritinib in standard UK practice to resemble those enrolled in the study. • Most important outcomes are reduction in disease burden (mast cells infiltration in bone marrow, spleen volume, serum tryptase, mutant KIT level), overall survival and symptom burden. Avapritinib therapy is associated with positive outcomes in all these parameters, as reported in the Pathfinder and Explorer trials • The Pathfinder and Explorer trials both reported clinically-relevant outcomes (either as primary or secondary endpoints), specifically clinico-haematological responses, spleen responses, patient-reported

	outcomes, and in the Explorer trial, OS and PFS estimates were also included. In addition the other disease burden markers reported (BM disease burden, mutant KIT allele levels and serum tryptase concentrations) are validated predictors of longer-term clinical outcomes which are included in the new ECNM-AIM response criteria (Gotlib et al, J Allergy Clin Immunol Pract, 2022 Aug;10(8):2025-2038). • I'm not aware of significant new AEs emerging since the trials were published
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	• No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA728]?	• Midostaurin, as appraised in TA728, remains the primary comparator for avapritinib. Other conventional treatments used in the UK for AdvSM include cladribine, interferon, hydroxycarbamide and imatinib. I am not aware of any relevant evidence relating to any of this published since TA728. • A trial of bezuclastinib in AdvSM is ongoing (Apex trial, NCT04996875) but only very preliminary data has been published in abstract form, and the agent is only available on study in 2 UK centres, so it is not a relevant comparator.
23. How do data on real-world experience compare with the trial data?	• Saunders et al (Blood, 2022; 140: Supplement 1: 3976–3977) reported on UK real-world experience of avapritinib for AdvSM accessed via a compassionate access programme. Outcomes were similar to the published trial data (overall response rate of 76.9%, median duration

	of response 16.6 months, normalisation of tryptase and spleen in 69% of patients
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	• I do not believe that any of the groups with the characteristics listed would be specifically impacted or disadvantaged by this therapy

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines The main comparator for avapritinib is midostaurin as a first-line (1L) treatment option. Best available therapy (BAT) is the comparator at second or subsequent lines (2L+) of therapy. However, this comprises a range of off-label therapies including imatinib, interferon alpha and other off-	• Given the extremely low incidence of AdvSM in the UK and the relatively poor efficacy of any agents currently available in the NHS for treatment after midostaurin failure, the consensus of UK clinicians is that choice of 1st and 2nd line therapy in this disease needs to be tailored to individual patient-specific factors. These factors include subtype of AdvSM, presence of KIT D816V mutation and other mutant clones, pace/symptoms/risk stratification of disease, patient age/fitness and social factors. There is no 'one-size-fits-all approach for these patients. For the majority of patients, I would select one TKI agent (either avapritinib or midostaurin, the choice between the two determined by the factors listed above) as 1st line therapy, and if patient doesn't respond or develops toxicities with 1st line TKI, I would switch to the alternative TKI as 2nd line therapy. Based on the available data, and from discussions with other AdvSM experts in the UK, I suspect avapritinib would be the favoured 1st line agent in many cases (if available), with midostaurin used as 2nd line

label therapies not included in the NICE scope. It also includes midostaurin, which is typically given at first line. Clarity regarding what therapies are given in the NHS after midostaurin and the proportion of patients receiving midostaurin as second or subsequent line therapy would be helpful.	agent if avapritinib fails. However there is likely to be a proportion of patients for whom midostaurin would be a favoured 1st line option, with avapritinib as 2nd line (see next section). If clinical trials are available (e.g. for novel TKIs) and patient is eligible, patients should be offered this option as well. • There are occasional situations when I might not use a TKI for 1st or 2nd line therapy: in patients with extensive disease bulk, particularly if there is rapid disease progression and severe cytopenias, cladribine may be considered, especially in younger fitter patients, but relatively high toxicities limit its use to a small subset of patients. Imatinib sometimes used but efficacy minimal except for the small minority (<10%) who are KIT D816V negative. Other treatments include hydroxycarbamide and occasionally interferon but they are usually used in the short-term palliative context, alongside supportive/ end-of-life care.
Issue 2: Separation of the population by treatment line The population in this appraisal has been separated according to treatment line, however NICE's recommendation for midostaurin is not restricted to 1L. Therefore, the EAG consider that treatment comparisons may not reflect the likely treatment pathway for	• The current treatment pathways for AdvSM are described above. • If in future avapritinib becomes available for NHS care, my view (which is shared by other mastocytosis experts around the UK who I've discussed this with), is that it would be helpful for both avapritinib and midostaurin to be available for 1st and subsequent lines of therapy. A line-agnostic approach for both agents would be allow haematologists to tailor 1st line therapy according to patient characteristics – for instance patients with rapidly progressive AdvSM, including those who may be eligible for allogeneic SCT if the effects of the SM can be reversed, would likely be recommended avapritinib, since it offers the prospect of rapid, deep disease debulking, minimising the likelihood of irreversible

advanced mastocytosis in the UK. Clarity around the likely treatment pathway in the UK would be helpful.	decline. It may also provide an opportunity for curative allogeneic stem cell transplant if the patient is otherwise eligible. A smaller subset of (often older) patients with slower-tempo AdvSM (especially pure aggressive SM) could have a trial of midostaurin, since this can be effective in this patient cohort – and if it doesn't work, avapritinib could be trialled. A permissive approach would also allow the choice of agent to be tailored according to risk of toxicities, based on patient's blood counts, baseline GI symptoms etc. So in essence a treatment pathway would include avapritinib and midostaurin as 1st and 2nd line therapies (alongside clinical trials), with other therapies (cladribine, imatinib, hydroxycarbamide) included as 3rd line and beyond. These views are shared by mastocytosis experts across the UK and will be formalised in upcoming UK BSH guidelines on the management of AdvSM.
Issue 3: Limitations of the effectiveness evidence There are no comparative studies of avapritinib. The effectiveness evidence comes from two single arm studies, of which one is completed and one is still ongoing and results are immature**.**	• AdvSM is such an exceptionally rare condition, clinical trials will necessarily be smaller than for most other haematological malignancies. Nonetheless, the data from the Pathfinder and Explorer studies (107 and 69 patients enrolled respectively) suggest that avapritinib therapy is associated with much better outcomes (in terms of disease burden reduction, overall survival and symptom burden) compared with historical outcomes. • In the latest update from the Explorer study (DeAngelo et al, Blood, 2022; 140, Supplement 2: 3932–3934), with a median follow-up of 45 months, median OS wasn't reached for 2 subgroups (mast cell leukaemia [MCL] and aggressive SM). For patients with SM-AHN the median OS was 46.9 months. Overall, 80% of patients had total clearance of mast cell (MC) aggregates form the bone marrow (BM), 99% had >50% reduction in tryptase, 75% had 50% reduction in KIT D816V levels, and 83% had >35% reduction in spleen volume.

	• Similarly, in the latest update from the Pathfinder study (Radia et al, British Journal of Haematology, 2024; 204, Issue S1: 4-35), with a median follow-up of 26 months, OS wasn't reached in any of the subgroups. Overall, 70% of patients had total clearance of MC aggregates from the BM, 61% had tryptase <20 ng/mL, 58% had KIT D816V VAF <1% and 74% developed non-palpable spleens • By contrast, in pre-KIT inhibitor era studies, median OS in MCL, SM-AHN and aggressive SM was 2 months, 24 months and 41 months respectively (Lim et al, Blood 2009: 113; 23: 5727–5736). • If more recent data from the Pathfinder and Explorer studies are available, this would be helpful • [*Update 15/6/24 following today's oral abstract presentation at European Society for Hematology Annual Scientific meeting by Dr Andreas Reiter, based on Pathfinder study with data cut-off of September 2023:* - with median follow-up of 38 months, median duration of response, PFS and OS were not reached for cohort overall; - for aggressive SM subgroup, OS was 93% at 36 months; - for AdvSM-AHN subgroup, OS was 70% at 36 months; - for mast cell leukaemia subgroup, OS was 72% at 36 months. All these OS estimates are much better than historical reports, and represent, in view, a step change in outcomes.]

Issue 4: Limitations of the indirect treatment comparisons There are uncertainties in the indirect comparison owing to limited reporting and inappropriate adjustment for baseline characteristics.	• Reiter et al (Leukemia 2022: 36, p2108–2120) have provided the only indirect comparison between avapritinib and BAT. The adjustment for baseline characteristics (including mutation-adjusted prognostic risk score, performance status, blood counts, number of prior therapies, age, sex, tryptase level, and AdvSM subtype) was defined up-front and appears appropriate to clinicians. The outcomes, principally OS, were significantly better in patients who received avapritinib than in those who received BAT. . As with any retrospective, notes-based study, the conclusions are less definitive than for an RCT, but are still of interest, especially in such a rare patient population, and suggest that avapritinib is an effective therapy in this disease, possibly more so than BAT. • If more appropriate adjustment for baseline characteristics is available, this would be helpful
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model There is a lack of consistency in the sources of data used to inform the different survival parameters in the model.	• I am not able to comment on this
Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations The OS data used in the company's base case analysis from PATHFINDER at the September 2022 data cut-off is	• In the pivotal midostaurin study (Gotlib et al, N Engl J Med 2016;374:2530-2541) the median follow-up was 26 months, with median OS of 28.7 months (33.9 months in the ITT population). In the Pathfinder 2024 update using the Sept 2022 data cut-off, the fact that the median OS wasn't reached for any of the AdvSM subgroups despite a median follow-up of 26 months (i.e. similar to the midostaurin cohort), in part reflects the efficacy of the drug.

immature, with median OS not reached in either population. The immature OS data is extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which lead to very different long-term survival outcomes.	The most recent Pathfinder data (EHA meeting 2024 – cited above) gives relatively mature OS data for this cohort of patients whose life expectancy has historically been very short: with median follow-up of 38 months, median duration of response, PFS and OS were not reached for cohort overall; - for aggressive SM subgroup, OS was 93% at 36 months; - for AdvSM-AHN subgroup, OS was 70% at 36 months; - for mast cell leukaemia subgroup, OS was 72% at 36 months.
Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS PFS was not available from the external control study to enable an inverse probability of treatment weighting (IPTW) comparison with PATHFINDER. Therefore, the company uses the comparator's TOT curve as a proxy for the comparator's PFS curve, but not for avapritinib. As a consequence, patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort	• I am not able to comment on this

Clinical expert statement

is off treatment before progression, whereas avapritinib is modelled to receive QALY gains for patients who interrupt treatment before progression, with no treatment costs after discontinuation.	
Issue 8: Source of evidence used to inform time on treatment in the model TOT for avapritinib is sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the Compassionate Use Program. The EAG considers the choice of TOT curve for avapritinib as a major limitation of the company's base case.	• The data from the Compassionate Use programme is based on relatively small numbers, but this reflects the extreme rarity AdvSM.
Issue 9: Uncertain duration of treatment benefit for avapritinib The duration of treatment benefit for avapritinib is uncertain. Insight into how long people may be expected to stay on avapritinib would be	• This will vary depending on the subtype of AdvSM. Based on the pooled analysis of the Pathfinder and Explorer studies (Gotlib et al, Blood, 2022: 140; 15: 1667–1673), the median duration of response for patients with SM-AHN, mast cell leukaemia and aggressive SM was 38.3 months, 21.6 months and not evaluable respectively. • At the EHA 2024 annual scientific meeting, the updated Pathfinder data were presented by Dr Reiter (data cut off Sept 2023) as an oral abstract. With a median follow-up of 38 months, median duration of response wasn't met. Whilst the number of patients still on

helpful, as this would allow for better estimation of its treatment benefit.	treatment wasn't reported, most responding patients would be expected to remain on avapritinib unless they developed major adverse events. According to the Reiter et al data, only 13% of patients on the study discontinued the avapritinib due to adverse events, implying the rest continued to take the drug so long as they were responding. Taken together, this suggests to me that probably >50% of patients were still receiving avapritinib at a median follow-up of 38 months and deriving benefit, but this is simply informed speculation. In keeping with this, a number of patients in my care have received avapritinib for over 3 years and their response continues to improve (clinically and KIT D816V response).
Issue 10: Exclusion of subsequent therapy The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment is not considered in the company's base case analysis in the 1L or 2L+ populations. Information on treatments used post-avapritinib discontinuation and numbers of people eligible to receive allogenic haematopoietic stem cell transplant would be helpful, along with information	• Therapeutic options after avapritinib will depend on the reason for failure (progression of the SM, progression of the AHN, toxicity) and include agents listed above (midostaurin, cladribine, imatinib, , hydroxycarbamide). With the exception of midostaurin (and occasionally cladribine), all these therapies are essentially palliative, aiming to control symptoms or blood counts, but have minimal effect on slowing disease progression. • In terms of allogeneic stem cell transplantation (alloSCT), the median age at diagnosis of AdvSM is around 64 years (Oni et al, Blood, 2019: 134; Supplement 1: 2960. Whilst fitness of alloSCT is determined by several factors, increasing age (especially >65 years) is a major factor associated with poorer outcomes, and consequently around 50% of patients with AdvSM are likely to be unfit for alloSCT on the grounds of age and comorbidities alone (or lack of suitable donor).

regarding post-progression survival outcomes for people with advanced systemic mastocytosis.	• Currently some younger patients may also be unfit for alloSCT due to SM-related organ damage or rapid deterioration/death due to progressive AdvSM, before an alloSCT donor can be identified. Effective treatment with avapritinib may increase the number suitable for alloSCT by improving the performance status of responding patients or controlling disease long enough to find a donor. By comparison, my experience has been that midostaurin is very unlikely to allow sufficient clinical improvement to permit alloSCT. It is possible therefore that, compared with midostaurin, avapritinib will facilitate potentially curative therapy with alloSCT in a very small cohort of patients who wouldn't otherwise be able to access alloSCT.
Issue 11: Uncertainty in the PF and PD health state utility values The utility values for the progression-free (PF) and progressive disease (PD) health states are uncertain. The utility data is based on the PATHFINDER September 2022 data cut-off (i.e., not the latest September 2023 data cut-off) where there are a limited number of observations at each time point used to inform the mapped utility value associated with PF in the 1L and 2L+ populations. Information about how quality of life would differ between	• Clinically I usually think of patients in terms of response to therapy: complete/partial response (CR/PR) versus stable/progressive disease (SD/PD). In my experience, patients experiencing SD/PD have very diminished quality of life – typically ascites, sarcopenia, malabsorption, splenomegaly, pancytopenia, and pleural effusions. Many are rendered immobile, dependent on others to complete activities of daily living, and some will require repeated hospital inpatient admissions to drainage of effusions, blood product support, treatment of infections etc. By contrast patients with CR/PR responses usually have experience significant improvements in organ function, quality of life, and independence in daily activities. The greater the disease response, the greater (usually) the improvement in these parameters. My clinical experience has been that avapritinib therapy seems to be associated with better disease response than midostaurin or other agents. • I think the health state PF includes patients achieving CR, PR but also SD, whereas PD includes only PD, obviously. So some patients with PF – i.e. those with SD – are likely to have significantly poorer QOL compared with other patients with PF – i.e. those with CR/PR. For this reason, The PF & PD stratification thus appears not to align precisely with clinical practice (if I have understood it correctly).

people who are progression-free and those who have progressive disease would be helpful.	
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Advanced systemic mastocytosis is an extremely rare and heterogenous form of blood cancer, usually associated with a very poor prognosis
- Current treatment options available in the NHS are limited: the only proven, available therapy is midostaurin but its use is limited by GI toxicity and moderate efficacy
- Two relatively small studies and a small UK real-world data set indicate that avapritinib is generally well tolerated and results in rapid debulking of disease in the majority of patients accompanied by marked reduction in the size of the malignant clone, with improvements in quality of life and organ (especially bone marrow and gastrointestinal) function
- Overall survival appears to be longer with avapritinib than with midostaurin, but follow up is still ongoing and there are no direct comparisons between the 2 agents

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with advanced systemic mastocytosis or caring for a patient with advanced systemic mastocytosis. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **14 June 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Part 1: Living with this condition or caring for a patient with advanced systemic mastocytosis

Table 1 About you, advanced systemic mastocytosis, current treatments and equality

1. Your name	Andrew Dugdale
2. Are you (please tick all that apply)	☒ A patient with advanced systemic mastocytosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced systemic mastocytosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	UK Masto
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced systemic mastocytosis? **If you are a carer (for someone with advanced systemic mastocytosis) please share your experience of caring for them**	I was diagnosed with Aggressive Systemic Mastocytosis (ASM) over 7 years ago. Both prior and post diagnosis, I have found my quality of life to be a very variable feast. At the beginning, no effective treatment existed, and life was extremely difficult, as I suffered from virtually all of the symptoms described in this submission to varying levels, but all at a level that effectively rendered me unable to work, socialise, or otherwise enjoy life. During the initial period, pre treatment, a number of 'off licence' drugs were trialled (including Interferon), however, none proved in any way effective against the ASM symptoms. In the second year post diagnosis, I was fortunate to get onto a compassionate use program with Novartis for Midostaurin, which I have been on since. Treatment with Midostaurin has been transformational, and I now have around 60% of my life where I can usefully contribute to society (still with significant limitations), but there is still find a significant amount of time where I suffer significant symptoms, mainly due to severe pain, fatigue, GI symptoms, or brain fog/memory related issues. I was forced to give up my job in 2017 due to ASM, but am now once again able to do some work (in a voluntary capacity), but with lower levels of reliability than would be ideal. Life with ASM is very difficult, as pre-planning any form of activity is full of risk. Masto in all forms is unpredictable, and this is one of the biggest issues for sufferers.. there is no way of saying "yes, I will be fine next Tuesday" for example, or "yes, I can go on that trip", as it is impossible to predict what Masto will throw at you 'on the day'.

	This make life for sufferers and their partners very different, restricting significantly the normal ebb and flow of life that is taken for granted by non-sufferers.
7a. What do you think of the current treatments and care available for advanced systemic mastocytosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**I am currently on Midostaurin, which whilst having been transformational for me, leaves room for improvement. The biggest issues with Midostaurin are the side effects (particularly nausea) which limit activity within a couple of hours of taking the drugs (which need to be taken twice daily). Also, fatigue remains a big issue, as well as a high risk of syncope in hot or cold environments, or if attempting exercise. It is also thought that Midostaurin may have been the trigger for my T2 Diabetes, and my onset of Paroxysmal arrythmia and Afib.** **So, whilst it is great that there is a targeted treatment available, there is room for new, improved, more targeted drugs, especially if there are reduced side effects associated.** **I have spoken to (a few) others on Midostaurin, and in my opinion, my experiences are at the better end of the drug performance spectrum. Midostaurin has controlled the primary ongoing measure of Masto (Tryptase) for me and reduced my level to within the normal range. So in respect of the core medical metrics, Midostaurin is performing very well for me.**
8. If there are disadvantages for patients of current NHS treatments for advanced systemic mastocytosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As previously stated, there are a number of down sides to Midosataurin, not least of which is the regular nausea, coupled with the ongoing fatigue, pain,etc (as described previously). Another issue is the need to take twice per day, with associated problems following each dose. Additionally, since being on Midostaurin, I have also required treatment for base of tongue cancer. The result of this (and the radiotherapy treatment to the throat) is that swallowing is not so easy anymore, and Midostaurin dosing requires four very large pills to be taken morning and night. At a personal level, this is a further draw back. Finally, the onset of T2 Diabetes and heart rhythm problems which are now being associated with Midostaurin, are two

	quite significant side effects, which could be seen as disadvantages. It is important to point out here, though, that the quality of life gain with the use of Midostaurin is worth the side effects no matter how severe..!
9a. If there are advantages of avapritinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does avapritinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a. I have no personal experienced with Avapritinib.** **9b. In conversation with a number of relevant medical practitioners, and accepting that the data set available is very limited, there appear to be a number of advantages to Avapritinib at this time. Not least for me is the smaller size of the tablets, and the reduced number and frequency of pills/doses per day.** **9c. It is my understanding that some immediate side effects (e.g. nausea) are reduced, and that there is a better disease outcome from this drug compared to Midosataurin, when considering disease metrics relating to the bone marrow findings.**
10. If there are disadvantages of avapritinib over current treatments on the NHS please describe these. For example, are there any risks with avapritinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no knowledge in this area and can make no appropriate comment
11. Are there any groups of patients who might benefit more from avapritinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I feel this question is premature due to lack of long-term data. Many of the key long term side effects of Midostaurin are only now becoming apparent (e.g. T2 Diabetes; and Arrythmia/Afib). As this data becomes clearer, then ideally patients susceptible to cardio electrical conduction problems, and those susceptible to T2DM would probably be best advised to avoid Midostaurin, and hence, perhaps favour Avapritinib. Although this is hard to say, as the long term side effects of Avapritinib are currently unknown.
12. Are there any potential equality issues that should be taken into account when considering advanced systemic mastocytosis and avapritinib? Please	NO

explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	It is important that this drug is approved, even though it is clearly difficult to meet NICE criteria when viewed through this particular application type.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines **We consider patient perspectives may particularly help to address this issue.** The main comparator for avapritinib is midostaurin as a first-	The simple answer here is that there are no clear cut BAT options for either Midostaurin or Avapritinib. Either drug is the other's first or second line option, based on the fact that there is no clear criteria for selecting one over the other, and as there are no second line therapies, the only BAT is 'the other drug'. Other drugs listed in the submission as BAT options, in fact are not BAT options as they are not disease modifying. Drugs such a Cladribine are only used as 'de-bulking agents' for occasional treatment of organomegaly; and in my personal experience, Interferon is not only ineffective, in my case it also increased the disease symptoms significantly (leaving me unable to eat for example). Imatinib is shown to be ineffective in 95% of cases where there is no KIT mutation.

line (1L) treatment option. Best available therapy (BAT) is the comparator at second or subsequent lines (2L+) of therapy. However, this comprises a range of off-label therapies including imatinib, interferon alpha and other off-label therapies not included in the NICE scope. It also includes midostaurin, which is typically given at first line. Clarity regarding what therapies are given in the NHS after midostaurin and the proportion of patients receiving midostaurin as second or subsequent line therapy would be helpful.	
Issue 2: Separation of the population by treatment line **We consider patient perspectives may**	Separation of population is helpful in understanding drug efficacy, but only where statistically valid population sizes exist and the efficacy parameters are clearly related to the drug being assessed. For Aggressive Systemic Mastocytosis, Avapritinib or Midostaurin would most likely be the 1st line and 2nd line; whilst for SM-AHN the treatment associated with the AHN may be the priority treatment, supported

particularly help to address this issue. The population in this appraisal has been separated according to treatment line, however NICE's recommendation for midostaurin is not restricted to 1L. Therefore, the EAG consider that treatment comparisons may not reflect the likely treatment pathway for advanced mastocytosis in the UK. Clarity around the likely treatment pathway in the UK would be helpful.	by Avapritinib or Midostaurin. For MCL, again, Avapritinib or Midostaurin are likely to be the primary (but potentially not sole) treatments.
Issue 3: Limitations of the effectiveness evidence There are no comparative studies of avapritinib. The effectiveness evidence comes from two single arm studies, of which one is completed and	The key takeaway here is that for all forms of AdvSM, Avapritinib or Midostaurin forms a key component of treatment, yet the outcome against each treatment line group is likely to vary based on external factors, making it hard in some cases to see the direct impact of the drugs, unless it is the sole treatment prescribed such as in the case of Aggressive SM for example. The challenge with viewing populations by treatment line to determine efficacy is that there are very small numbers of each type of patient anyway, so getting a significantly large enough population for each treatment line on which to accurately base outcome analysis is extremely difficult. This is further compounded by determining which drug is affecting which factor where multiple drugs are being used.

Patient expert statement

one is still ongoing and results are immature.	
Issue 4: Limitations of the indirect treatment comparisons There are uncertainties in the indirect comparison owing to limited reporting and inappropriate adjustment for baseline characteristics.	I do not feel qualified to comment here
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model There is a lack of consistency in the sources of data used to inform the different survival parameters in the model.	I do not feel qualified to comment here
Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations The OS data used in the company's base	I do not feel qualified to comment here

Patient expert statement

case analysis from PATHFINDER at the September 2022 data cut-off is immature, with median OS not reached in either population. The immature OS data is extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which lead to very different long-term survival outcomes.	
Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS PFS was not available from the external control study to enable an inverse probability of treatment weighting (IPTW) comparison with PATHFINDER. Therefore, the company uses the comparator's TOT curve as a proxy for the comparator's	There are no clearly defined standards for PFS for all three types of AdvSM. Without this, researches have to use other compromised proxies. It was clear from the recent 'expert clarification call' that there is in fact no clarity around what is defined as PFS – the discussion centred on 'opinions'. Hence, in my opinion, it would be likely deemed reasonable to use TOT as a proxy for PFS, as TOT is an absolute value that can be clearly defined, so can be examined and tabulated.

Patient expert statement

PFS curve, but not for avapritinib. As a consequence, patients in the comparator arm discontinue treatment due to disease progression only and therefore no part of the cohort is off treatment before progression, whereas avapritinib is modelled to receive QALY gains for patients who interrupt treatment before progression, with no treatment costs after discontinuation.	
Issue 8: Source of evidence used to inform time on treatment in the model TOT for avapritinib is sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the Compassionate Use Program. The EAG considers the choice of TOT curve for avapritinib as a major	I believe my comments re Issue 7 apply here also. Without any definitions of PFS in each treatment line, TOT is a viable proxy.

Patient expert statement

limitation of the company's base case.	
Issue 9: Uncertain duration of treatment benefit for avapritinib The duration of treatment benefit for avapritinib is uncertain. Insight into how long people may be expected to stay on avapritinib would be helpful, as this would allow for better estimation of its treatment benefit.	I do not feel qualified to comment here
Issue 10: Exclusion of subsequent therapy The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment is not considered in the company's base case analysis in the 1L or 2L+ populations. Information on treatments used post-avapritinib discontinuation and	I do not feel qualified to comment here

numbers of people eligible to receive allogenic haematopoietic stem cell transplant would be helpful, along with information regarding post-progression survival outcomes for people with advanced systemic mastocytosis.	
Issue 11: Uncertainty in the PF and PD health state utility values **We consider patient perspectives may particularly help to address this issue.** The utility values for the progression-free (PF) and progressive disease (PD) health states are uncertain. The utility data is based on the PATHFINDER September 2022 data cut-off (i.e., not the latest September 2023 data cut-off) where there are a limited	Again, I feel that my answer to Issue 7 is applicable here. Where PF or PD criteria remain undefined, uncertainty is the only possible state. The research base around Mastocytosis is growing, but I have not yet seen research focused on defining the core criteria required in order to obtain standardised results when analysing disease outcomes – especially based on PF or PD outcomes. I am, however, a lay person here, and as such am simply presenting my own perspective, (rather than a perspective of a medical research expert), based on my 7 years as an AdvSM patient with a high interest level in researching and understanding my own disease.

number of observations at each time point used to inform the mapped utility value associated with PF in the 1L and 2L+ populations. Information about how quality of life would differ between people who are progression-free and those who have progressive disease would be helpful.	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- All the data available on AdvSM has uncertainty, as there are very few patients available to research in each treatment pathway.
- The uncertainty is further compounded by lack of clearly defined and agreed definitions in areas such as ‘what constitutes PF or PD’ disease
- Research has been carried out over time, with different criteria being applied at different stages of the research as more knowledge is gained.
- Expecting ‘standardised data’ with high levels of certainty and accuracy is therefore unreasonable
- Allowance needs to be made in the approval process for these high levels of uncertainty and the ongoing lack of standardised research in this field

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with this condition or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **30 July 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Part 1: Living with this condition or caring for a patient with advanced systemic mastocytosis

Table 1 About you, advanced systemic mastocytosis, current treatments and equality

1. Your name	Sue Rudland
2. Are you (please tick all that apply)	☐ A patient with advanced systemic mastocytosis? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced systemic mastocytosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Uk Mastocytosis Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced systemic mastocytosis? **If you are a carer (for someone with advanced systemic mastocytosis) please share your experience of caring for them**	Pre-Diagnosis I lived life happily in the fast lane with 18hour productive days. I had a high-powered job as well as caring for my brain injured daughter and her young son. In the January I started to feel unwell and spent the following 10 months deteriorating whilst undergoing investigative tests. I gave up my employment in the April, as I could no longer cope. My initial symptoms of mild fatigue, night sweats and generally feeling unwell, soon escalated to; chronic fatigue, bone pain, stomach cramps, breathlessness, unable to function, unable to cook, complete household tasks, dress or bathe myself. I stopped caring for my daughter and family had to step in to help, I stopped driving and my husband became my carer who wheeled me to hospital appointment (I couldn't manage the walk along the hospital corridors). A series of blood test tryptase and BMB confirmed my mast cell count exceeded 800. My family were beside themselves with worry, the matriarch was sick, really sick. One day my husband came home unexpectedly early from work finding me collapsed and administered my epi pen, which saved my life. I had 9 emergency admissions to hospital for idiopathic anaphylaxis in the following 8 weeks. I felt a pending sense of doom as my strong will was leaving me. The only way I can describe living with ASM is going from the fast lane to slow lane and then at a standstill on the hard shoulder within weeks. The impact was far reaching, I could no longer care for myself let alone my daughter and grandson. My husband of 40 years was devastated and living on tenterhooks waiting for the next collapse, he subsequently had a stroke after my 9th emergency admission, he never worked again. The strain of living with ASM was the lack of knowledge of my condition. No one in my local NHS hospital understood ASM and that made us all feel very unsafe. Avapritinib was my saving grace, it reduced my mast cell count from 800> to <50 in 9 months. This stopped the

	anaphylaxis and I recovered. It prepared me for a stem cell transplant. But for the Avapritinib, I would not be here. My family would have lost a mother, grandmother wife and my grandson and daughter with her complex needs would have been a significant burden to Social Care Services, to replace the 70 hours of care that I gave them each week.
7a. What do you think of the current treatments and care available for advanced systemic mastocytosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) I only know of Midostaurin and have heard it makes patients sick. I don't know how you can function if you are constantly being sick? I was never sick the only side effect was I had from Ava was weight gain and a bit of swelling, certainly nothing that interrupted my daily life. b) One male patient's son reached out to me. He had the same diagnosis as me (ASM/CMML) he told me his father had several hospital admissions; his health had declined the same as mine. His dad did not respond well to Midostaurin and had to stop taking it.
8. If there are disadvantages for patients of current NHS treatments for advanced systemic mastocytosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The patient I know of, didn't get any benefit from Midostaurin and had to stop. I am only grateful that I had Avapritinib and this did not happen to me.
9a. If there are advantages of avapritinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does avapritnib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Avapritinib worked for me and I felt the benefits within weeks. It was to my mind the golden bullet that targeted my kit gene, enabling me to become strong enough to undergo chemotherapy and a stem cell transplant and subsequently disease free of CMML and in remission. If it was for Ava I don't think I would be here. I'm now living life to the full, I'm able to comfortably care for my daughter and grandson a) Midostaurin makes people sick not well b) My interaction with a patient being treated with Midostaurin tells me it doesn't work for everyone. Avapritinib worked and made me well quick. It prepared and conditioned me for chemo and a stem cell transplant. c) You are ill enough without suffering treatment side effects that debilitate you further. Midostaurin is gruelling and doesn't prepare you for transplant.

10. If there are disadvantages of avapritinib over current treatments on the NHS please describe these. For example, are there any risks with Avapritinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Swelling and white hair which soon changed to all sorts of shades of grey!
11. Are there any groups of patients who might benefit more from Avapritinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Defer to Specialists
12. Are there any potential equality issues that should be taken into account when considering advanced systemic mastocytosis and Avapritinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Defer to Specialists

13. Are there any other issues that you would like the committee to consider?	The speed of recovery? I improved within weeks of being treated with Avapritinib. Feeling stronger less breathless less fatigue. It stopped my emergency hospital admissions for anaphylaxis which was idiopathic (9 in 8 weeks) and overall reduced the burden on the NHS and other agencies. My BMB should a reduction in mast cells from 800> to <50 in months

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Avapritinib is a gold bullet for those with the Kit gene
- Recovery was swift, with minimal side effects and it stopped my anaphylaxis
- Avapritinib is a catalyst to enable a stem cell treatment pathway to progress
- Without it I would not be here
- Without me, my brain injured daughter and her dependent son would become a financial burden on social care and other agencies. I therefore deem Avapritinib an investment - not a cost.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **14 June 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 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)	The UK Mastocytosis Support Group
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	UK Masto: Blueprint Medicines: Honorarium for 1 trustee and 1 volunteer to participate in the steering committee meeting for design of a survey on quality of life in mastocytosis patients, and then for discussion of data and publications plans: £1350 Honorarium for trustee to participate in a meeting of European leaders of patient groups: £294 These were one-off payments for particular activities.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines	Yes	Our response is informed by discussions with clinicians in the past (5 consulted in summer 2023 for scoping) and since receiving these TE questions (3 consulted), as well as knowledge of the experience of patients with ADVSM and their treatment experiences (previous surveys, new June 2024 small survey, and interactions with patients over time). Treatments given after midostaurin: The options if midostaurin is no longer suitable (either due to side effects or because it has never or is no longer keeping the mastocytosis controlled) are either another TKI via CUP or trial (if eligible and available) or cladribine. Example 1, a patient with SM-AHN has not responded to midostaurin over several months and blood counts are too low for the Apex trial (bezuclastinib—a newer 2nd line (targeted) TKI). Patient is being given cladribine to rapidly reduce the burden of mast cells in the liver and spleen with the hope that blood counts will recover, and the trial drug can be offered. The cladribine is being used for a specific purpose (debulking) with the understanding that it is not disease modifying in the longer term. 1-2 cycles is the typical duration.

		Example 2, a patient with ASM received interferon (before midostaurin was available) with no change in bone marrow infiltration, splenomegaly or explosive diarrhoea. Midostaurin was used for 1 year. Patient reports, “My tryptase had started going up and I also had severe nausea daily with sometimes vomiting. I stayed on it with the hope that time would lessen side effects, but it never did.” Because of the rising tryptase the patient stopped midostaurin. The patient had a two-week period on no targeted therapy, during which time “the mast cells surged back with some symptoms surging greatly, especially hot flushing.” The patient then moved to avapritinib. Now that midostaurin is available in the UK, experienced haematologists would not have used the interferon, so would go from Midostaurin to a 2nd line TKI (in trial) where possible according to the haematologists we consulted. Midostaurin as second line therapy: Two patients described to us having had interferon first line (before midostaurin was available) with considerable side effects and little or no change in symptoms and no change to underlying markers of disease, and then having midostaurin. One of these patients continues on midostaurin despite daily nausea and the other is patient 2 above, who had to come off midostaurin because tryptase was rising, and avapritinib is being used in 3L. Another scenario that UK haematologists describe is one in which cladribine is used 1L for rapid debulking of the liver and spleen, followed by midostaurin (or a trial 2nd generation TKI). Cladribine might also be used first where there are significant cardiac issues. Midostaurin might be used as a second therapy in a patient with an AHN if the AHN more urgently needs addressing, but we are assuming that by second line it is meant treatment for the SM component of SM-AHN, not the AHN.

In our small survey of patients (June 2024) we found the following order of treatments:

Diagnosis	Tx 1	Tx2	Tx 3	Tx4
ASM	Interferon (pre-midostaurin access	Midostaurin	Avapritinib	
SM-CMML	Avapritinib	Bone Marrow Transplant		
SM-PV	Avapritinib			
SM-CMML	Avapritinib	Bone Marrow Transplant		
ASM	Interferon (pre-midostaurin access)	Midostaurin		
ASM	Imatinib (before D816V mutation identification)	Avapritinib		
ASM	Cladribine	Interferon (pre-midostaurin access)	Midostaurin	Avapritinib
ASM	Midostaurin	Avapritinib		

		We cannot speak to whether these are representative of the treatments received across the UK, though the patterns are consistent with what the haematologists we consulted have described.
Issue 2: Separation of the population by treatment line	Yes	We understand that the haematologists in the UK are working to elucidate the treatment pathways. The release of the 3-year data on Avapritinib at EHA this past week is likely to influence that pathway. Avapritinib still had not reached Median OS (median follow up of 38 months) in all forms of AdvSM, a stable ORR and a slightly higher CR and CRh than the earlier data cut. The haematologists we consulted said midostaurin might be used at 1L in patients with cytopenias or cardiac failure.
Issue 3: Limitations of the effectiveness evidence	No	Our only observation here would be that AdvSM is a group of rare diseases and so there will be uncertainty. We recognise that the STA process is better suited to conditions where it is possible to have more certainty. Having been involved in the STA for midostaurin we are pleased to see that there is a larger trial to draw data from with Avapritinib to support the assessment. We are pleased the 3-year data is now being brought into the assessment.
Issue 4: Limitations of the indirect treatment comparisons	No	We are also grateful that there is a published retrospective comparison of avapritinib v midostaurin (Pilkington, 2022), something that was lacking when midostaurin was being assessed.
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model	No	We have nothing additional to add here.
Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations	Yes	Having seen the updated data (3-yr) that was presented at EHA this past week we can see that the OS data remains stable with slightly improved CR and CRh as compared to the previous data cut. This is consistent with what patients report in our small surveys and in their interactions with us. Responses have remained good.

Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS	No	We do not have additional data to predict time on treatment. We understand from the haematologists we have consulted that 5-7 years is considered to be a reasonable assumption based on current data.
Issue 8: Source of evidence used to inform time on treatment in the model	No	We do not have additional data to predict time on treatment. We understand from the haematologists we have consulted that 5-7 years is considered to be a reasonable assumption based on current data.
Issue 9: Uncertain duration of treatment benefit for avapritinib	Yes	We know of one midostaurin patient who has been on it for more than 10 years, but the diagnosis may have been more like smouldering SM (a less aggressive disease which didn't have that name yet back then) and perhaps the early use has led to this long survival and continued use Here are the comments from our June 2024 survey regarding experiences with Avapritinib for patients where we know the duration of treatment. "Ava was a Godsend. All the above [flushing, itching, skin spots, fatigue, abdominal pain, vomiting, nausea, enlarged spleen/liver, anaphylaxis, short temper and anger] eventually went away!!!!. Game Changer." [Entered Pathfinder Trial in 2021 and still in CR and taking avapritinib.] "Avapritinib gave me not only my life but a real chance of a cure, I was able to have a stem cell transplant from my brother. I will be forever grateful to that tiny little tablet. I have since walked one of my daughters down the aisle, I have a 3rd grandson and granddaughter to… [Stable 1 year after BMT. Avapritinib for 1 year.] "If I had not have had Avapritinib I would have no quality of life whatsoever, my daughter and my grandson would be under the care of the local authorities… Avapritnib restored ever fibre of my being. It brought my mast cells under control and thereby stopping the re-occurring stubborn anaphylaxis… [T]his stopped the repeated hospital admissions which must have saved my local hospital money [8

		episodes of anaphylaxis over nine weeks]. I was in hospital more than I was at home. In one particular day I was discharged and then rushed back by ambulance 30 minutes later, the cost to the NHS was significant." [Stable 10 months after BMT. Avapritinib for 16 months.] "Had few masto symptoms on 100 dose; when I had to drop to lower doses due to blood labs impacts, some itching and flushing started coming back." [A patient for whom midostaurin was stopped due to poor tolerance (nausea) and poor control of mastocytosis has been on Avapritinib for two years but has reduced the dose from 100mg to a dose that toggles between 50mg and 25mg ever other week due to cytopenias.] "Midostaurin, as the only treatment I can talk about knowledgeably, has been like a miracle. However, it is an incomplete miracle and there is still a lot of room for improved drugs in this field. Some issues were almost resolved, such as Anaphylaxis, GI issues, asthma issues, skin issues, itching was totally resolved (although some are creeping back now); some issues were not improved, (most notable being pain, syncope, dizziness); some issues have continued to progress (osteoporosis being the most notable); and new issues have been introduced (T2DM, stage 1 liver damage and arrythmia/afib being notable examples). Overall, I am better able to discharge day to day living on Midostaurin, but I still regard myself as disabled, even on the targeted therapy. For example, I still regard a day out in town as 'am expedition' that needs careful preparation and planning. Spontaneity in life has still not been recovered, despite the targeted therapy… so life is different and requires care." [Midostaurin for 5 years]
Issue 10: Exclusion of subsequent therapy	Yes	We understand from conversations with UK haematologists that in SM-AHN (who comprise about 70% of the AdvSM patients) the progression tends to be in the AHN if the patient has received a 2nd generation TKI such as Avapritinib or Bezuclastinib, not in the SM compartment. These patients are the ones who are most likely to then go to transplant. Since midostaurin does not prepare SM patients as thoroughly for transplant, outcomes have improved with the use of

		avapritinib if a CR is achieved prior to transplant. (McLornan et al Allogeneic haematopoietic cell transplantation for advanced systemic mastocytosis: Best practice recommendations on behalf of the EBMT Practice Harmonisation and Guidelines Committee. Leukemia. 2024). We do not have additional data on the proportion of patients going to transplant, or progressing, but data from midostaurin would not be relevant for the transplant question given the difference in outcomes between patients prepared with midostaurin and with avapritinib.
Issue 11: Uncertainty in the progression-free and progressed disease health state utility values	Yes	This is a challenging exercise given the small number of patients overall and the very small number who have had experienced being Progression-Free and then having Progressed Disease; since PD often leads to death there are few people to ask for responses. It would take more time than we have had available to address this in a way that leads to a robust numerical response, but in response to this TE request we have surveyed some advanced SM patients and asked them to describe their experiences, using the EQ5-D dimensions to guide comments. One patient has had a TKI (midostaurin) stop working and had a brief return of some symptoms before avapritinib started to work. In other cases where the patients have not had the experience of having progressed disease after a period of being progression-free we asked them to imagine the scenario of returning to the symptoms they had before they received targeted therapy. Here are a selection of responses that we think help elucidate the difference between controlled and uncontrolled Advanced SM. **1. <u>Usual Activities (work, study, housework, family or leisure activities)</u>** <u>Progression-Free Scenario</u> “I am progression free now it is life changing in words that are beyond description. You simply have no idea of how debilitating this illness can be. I can freely do my housework. My family commitments are demanding. I have a brain injured daughter and I care for her son as she recovers... I care for both of them, and I

		care for my husband who has had a stroke. I am able to do all of these with energy to spare. I am able to mix with family again and attend family weddings and functions and have lunch with my friends. My life is like night and day. It's an amazing transformation and I could not be more happier than I am right now, thanks to Avapritinib." "Could happily carry out all activities" "Improved ability to do these things" "It would allow at least a partial return to 'normal' life" <u>Imagining Progressed Disease Scenario:</u> "It is important that you understand who I am before I explain how this would affect me. I was a very controlled powerful, confident businesswoman and in my personal life, the go to person for the family and extended family and friends. I was there for everybody, and I was happy to be that person I was more than capable of doing whatever was required to solve problems, to organise events, to rally the troops. The fear of my symptoms returning is real. It is the worst thing that could ever happen to me and the worst thing that could ever happen to my family. I am now a full-time carer for my daughter who sustained a brain injury and I care full-time for her son and look after my husband who had a stroke and I am more than capable of doing all of those things but if my symptoms return I could do none. I know what that feels like when I had the symptoms before I could do no housework. I could not study. I could not go out. I could not mix. Getting from the bed to the toilet was as much as I could manage and I needed help to help me out of bed. I really do not want those symptoms to return. I am scared, having been through it. I do not want the anaphylaxis to return. I have suffered for eight hours at a time in A&E with my husband pleading with them, to recognise the anaphylaxis…

		I survived nine anaphylaxis in eight weeks. There would be no quality of life should be symptoms return. “I would be unable to carry out any activities, I would just be existing rather than living.” “Would need more rest.” “Note: I am getting some returning symptoms on Midostaurin - starting with GI and skin issues. But for the purposes of this question, I will imagine fatigue is the worst. It would reduce once again my ability to carry out daily activities.” **2. <u>Self-Care (Washing and Dressing)</u>** <u>Progression-Free Scenario:</u> “I am now able to bath myself to wash myself to dress myself to do my own make up and my hair to stand still in front of the mirror long enough. to do my make up.” “Could comfortably look after myself” “It would enhance my ability to take care of myself and reduce my need for support of others.” <u>Imagining Progressed Disease Scenario:</u>

		"I would not be able to wash myself. I would not be able to dress myself and getting dressed would take 45 minutes as every time you lift a limb you then need to rest afterwards how chronic the fatigue is. I would wash with a hot flannel and a bowl of water at the side of my bed getting into a bath would be an impossible and standing still in the shower would be impossible too." "Showering very difficult the pressure of water would agitate my rash." "It would clearly reduce again the ability to be independent" **3. <u>Anxiety/Depression</u>** <u>Progression Free Scenario:</u> "I am very free. I do not live with the fear that my family will have to do without me. I live for full life. and I could not be happier." "I would be happy and living life to the full, enjoying every day." "It would reduce significantly my mental stressors and increase feelings of well being" <u>Imagining Progressed Disease Scenario:</u> "When your strength has left you your will starts to leave you and self doubt is a burden. The worry of others around you becomes a burden. The fear of the future becomes a burden and it's hard to think of anything else in your waking hour. This is so draining that all you want to do is sleep."

		"I would be living permanently under a dark cloud." "Would worry about symptoms" "It would negatively affect my moods to a large extent." **4. <u>Mobility</u>** <u>Progression-Free Scenario</u> "I do have bone damage and occasionally I am under the osteopath but it is a small priced pay considering where I have come from. I had no independence whatsoever and I could barely walk from a sofa to a bed now I am out with the girls and can do lunch." "No problems getting about" "It could improve mobility, depending to what level mobility issues (e.g. syncope, dizziness, pain, reaction to temperature/sun etc. were resolved)." "I get to exercise aggressively without fear of stomach pain." <u>Imagining Progressed Disease Scenario:</u> "Bone pain makes it incredibly difficult to walk and get yourself around the house without help. I would be unable to stand in the same position for more than 30

		seconds. I would need to sit back down if not late. I remember before treatment I would venture from the living room on the sofa and have to stop off at the kitchen table and set to rest before making it to the bedroom and lay on the bed exhausted, from the journey and I live in just small two bedroom bungalow." "Would feel fatigued and tired." "Again, depends on what symptoms return, but whichever return, it is likely to have a negative effect on mobility." **5. Pain** Progression-Free Disease Imagining Progressed Disease Scenario: "There is no warning when you have bone blasts they are painful and awful. You can have so many in a day that it makes you want to just cry because it breaks you but you have to keep going. I would have pain in my spleen and in my liver so forever holding my sides. I would have pain in my throat from indigestion after eating food because my stomach was pressured by the enlarged spleen." "Not so much pain but permanently uncomfortable, restless, tired, not eating, depressed." "GI Pain" "Pain has not stopped even on Midostaurin. I am still on almost as much pain medication as before treatment with targeted therapy drugs."

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **14 June 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 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)	Nominated representative for British Society of Haematology (BSH)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	1. **Blueprint Medicines** **£20k approximately total** **I am a member of the study steering and response adjudication committees (SSC and RAC) for the EXPLORER and PATHFINDER trials: Avapritinib in Advanced Systemic Mastocytosis – fees for committee meetings.** **Advisory board for BPM** **Educational sessions - honoraria and travel/ accommodation if presenting at symposia/posters/oral presentations.** **Ongoing member of SSC/RAC – ongoing fees for PATHFINDER.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines	**No**	There are limited effective therapeutic options for patients with Advanced Systemic mastocytosis (AdvSM) and more complicated by the fact that the majority of patients with AdvSM (>70%) are in the category of Systemic mastocytosis (SM) with an associated haematologic neoplasm (SM-AHN). This means that each patient needs to be individually assessed for prognosis regarding the 2 co-existing haematological neoplasms to then formulate a personalised treatment and monitoring plan. SM treatment options: With the current evidence base and data for this rare haematological neoplastic disease – the tyrosine kinase inhibitors (TKI) are the only targeted therapy that has been shown to have disease modifying effects: decrease in mast cell disease burden as evidenced by decrease in spleen size, decrease on serum tryptase levels and bone marrow mast cell burden. These have also been associated with a significant improvement in quality of life (symptom burden measured in trials). Midostaurin and Avapritinib have demonstrated their efficacy and improvement in overall survival. The advantage of Avapritinib over Midostaurin is that patients achieve complete remission/ complete remission with partial haematological

		recovery which is not seen with Midostaurin, where major and partial remissions have been reported. Cladribine has been used as a cytoreductive agent with partial and temporary responses reported in patients and debulks high mast cell disease burden if these patients are unable to access TKI – if profound cytopenias (low platelet count < 50 x 10^9/l will preclude use of Avapritinib and significant cardiac dysfunction / failure would preclude use of Midostaurin & Avapritinib). Patients have been reported to have decrease in spleen size but in the AdvSM cohorts no significant decrease in tryptase levels have been sustained and there is an increased risk of infections due to prolonged cytopenias associated with Cladrabine. Best available therapy as second line if Avapritinib was utilised as first line would depend on whether the SM component or AHN component needed treatment / if the need for change was due to intolerance for each individual patient For SM disease management and their disease status/ blood counts at time of need for change of treatment. Midostaurin could still be used as second line. Cladrabine could still be an option. Currently these are rare cases and are discussed with clinicians with experience on an individual case by case basis. A UK guideline writing group of the management of adult patients with SM has been established and work is being started to develop guidance. Currently the updated US NCCN Guidelines were recently published: Version 3.2024. Gotlib et al. J Natl Compr Canc Netw 2024;22(2D):e240030 doi:10.6004/jnccn.2024.003 These guidelines are comprehensive and place both the TKIs as first line equally with clinical trials as options for all AdvSM subtypes with other recommended regimes including Cladrabine/PegIFN.

		In my personal experience this should be similar in UK practice. The 'goal' for what the anticipated outcome for each patient will guide which is first line – Midostaurin/Avapritinib. The decision will be informed by: Age of patient and co morbidities Prognosis of SM – risk assessment AHN component and prognosis Whether allogeneic haematopoetic stem cell transplant should be considered
Issue 2: Separation of the population by treatment line	Yes	If we look at the 3 sub categories of AdvSM: Aggressive SM (ASM), SM-AHN and Mast cell leukaemia (MCL) and the recently presented 3yr follow date from PATHFINDER. (EHA 15th June 2024). 107AdvSM (20% ASM, 66% SM-AHN and 14% MCL) patients were treated with Avapritinib 200mg od starting dose in 105 patients. Median follow up of 36 months. Median age 68yrs (range 31-88yrs). 58% male. 26% ECOD PS2/3. 64% had received previous lines of treatment – some > 1 majority included Midostaurin/Cladrabine. 83/107 patients were evaluable by the m IWG-MRT-ECNM criteria. The overall response rate (ORR) was 73% (63-83). ORR in treatment naïve patients was 87%(69-96) i.e. Avapritinib first line. ORR is those who have prior treatment was 66% (52-79) Similar responses were observed across all subtypes with a deeper response in those with pure ASM and MCL i.e. with no AHN. CR/CRh was reported in 29% with CR/CRh noted to be 43% in treatment naïve patients compared to 21% in those who had prior treatment.

		Progression rate was reported at 17% (18/107 patients) in the AHN component only so ASM/MCL patients have not shown any progression to date in the trial. Median overall survival has not been reached in any of the subtypes in AdvSM and regardless of exposure to prior therapy. This demonstrates superior improved outcomes, sustained and deeper responses with Avapritinib as first line TKI therapy compared to second/third line but still able to increase depth of responses in patients who have been previously treated. Ref: Reiter et al. Avapritinib in patients with advanced systemic mastocytosis(ADVSM): Efficacy and safety analysis from the Pahse 2 PATHFINDER study with a 3-year follow up. HemaSphere 2024;8(S1): Abstract (S224)
Issue 3: Limitations of the effectiveness evidence	Yes	AdvSM is extremely rare and the evidence presented in the current trials with EXLORER and PATHFINDER – numbers of patients recruited internationally provides to most robust data currently in terms of safety and efficacy of Avapritinib. 107 patients in phase 2 PATHFINDER and 69 in Phase 1 EXPLORER demonstrating efficacy and safety. Now with 2 and 3 yr follow up data adding to efficacy as outlined in issue 3 response. The effectiveness of Avapritinib as a disease modifying targeted TKI is evidenced in the ORR and depth of reduction in mast cell disease burden: reductions in spleen size, tryptase levels, bone marrow disease burden and C-KIT variant allele frequencies. The former 3 are reflected in the m IWG-MRT-ECNM response criteria. UK experience with compassionate use Avapritinib presented at ASH 2023 of 13 patients to demonstrate real world experience in UK showed 10 patients with Avapritinib first line and 3 with prior treatments (Midostaurin, Cladrabine and

		Azacytidine). The responses mirrored those of the PATHFINDER 2 yr data: ORR using the m IWG-MRT-ECNM criteria was 76.9% with 53.8% of patients achieving a CR/CRh. Progression was noted IN AHN component in 1 pt at time of reported, in SM component in 1 patient. Ref: Saunders et al: The use of Avapritinib in advanced systemic mastocytosis : Report of an open label compassionate use program in the UK. Blood (2022) 140(Supplement1): 3976-3977
Issue 4: Limitations of the indirect treatment comparisons	No	With the TKIs showing superiority and efficacy over cytoreductive options there will not be a place for direct comparisons. However, the data from the paper published by Reiter et al: Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukaemia (36) , 2108-2020 (2022) has the most number of patients and in 6 international institutions including the UK. 176 patients in PATHFINDER with Avapritinib treatment vs 141 in the BAT arm with retrospective review of notes. The overall results showed super results with Avapritinib for overall survival in the whole population, OS in those treated with 2 more lines of therapy and duration of treatment. The limitations of this analysis: Trial study data being compared with real world retrospective notes / data -latter not as robust as trial data. However, the centres involved were centres of excellence with experience in managing patients with AdvSM so overall data sets and definitions applied and diagnostic/prognostic criteria should not have been a significant issue. This real-world data was likely to be more robust data from these centres than from smaller centres with limited experience. Confounders such as duration of treatment and efficacy over time in retrospective review with variations in the population sizes will have also had an impact. However also basing my response in my clinical experience of treating SM for > 15 years and also including data from the UK centre benefit of avapritinib over the BAT arm were seen in patients in clinical practice with improvement in symptoms

		and efficacy of Avapritinib and better side effect profile leading to increased tolerability and therefore duration of treatment.
Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model	No	Unable to comment as different metrics used as experience with Avapritinib demonstrated good outcomes and challenging to apply these to such a heterogenous population of patients under the umbrella of AdvSM.
Issue 6: Immaturity of the overall survival (OS) data used in the extrapolations	Yes	The data with 3 year follow up showing OS survival rates not reached across all subtypes is more mature than the 2 year data and still compelling with respect to efficacy and maintained ORR over the additional year.
Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment (TOT) as a proxy for PFS	Yes	Again referring to the 3 yr follow up data presented 15.6.24 – the results show that progression occurs in 17% of patients and predominantly in the AHN component. Similar data was presented from the EXPLORER study in 2021 (Deninger et al) noting that progression was seen in approximately 20% of patients who has high risk AdvSM and noted to be in the AHN compartment predominantly. TOT as a proxy for PFS seems a reasonable alternative.
Issue 8: Source of evidence used to inform time on treatment in the model	Yes/No	Unable to comment
Issue 9: Uncertain duration of treatment benefit for avapritinib	Yes	At this time point using the 3 yr data as a baseline, I would consider that the duration of treatment benefit would be 5-7 years. The OS survival reported at 36 months (95% Ci) was 75% (66-83) in all 107 patients, 93% in ASM patients (79-100), 70% in SM-AHN(59-81) and 72% in MCL (71-100) with median OS not reached for all subtypes regardless of prior treatment lines. Those patients without an AHN likely to have a deeper and longer duration of response

Issue 10: Exclusion of subsequent therapy	Yes	It is difficult to define what subsequent lines of therapies might as will differ for individual patients and will need to be personalised in view of the heterogeneity of the AdvSM disease spectrum. In general: The progression of AHN will need AHN directed treatment. There are few SM progressions noted to date on PATHFINDER/EXPLORER. The option of allogeneic stem cell transplant as a curative option may not be available to many patients and will be dictated by their disease status – SM-AHN with high risk mutations, age, comorbidities and availability of potential donors. Recent retrospective dataof 71 AdvSM pts who underwent an allo HSCT from the German group (Lubke et al: Leukemia 20204;38(40: 810-821.) showed on multivariant analysis that the success of the transplant depended on the depth of response and SM disease burden ie those with CR/CRh or good PR with respect to their SM disease burden had a better outcome and 2nd generation TKIs are able to achieve deeper responses. In addition, EBMT best practice consensus guidelines have been developed in parallel with respect to consideration of TKI and allo HSCT in SM. (McLornan et al. Leukaemia. 2024 Apr: 38(4):699-711. These also reflect on the impact of TKI – 1st and 2nd generation in reducing the SM disease burden as well as other considerations to move to allo HSCT or not.
Issue 11: Uncertainty in the progression-free and progressed disease health state utility values	No	Unable to fully comment as difficult to fully appreciate / understand the disease health utility values. Patient experiences and transformation of their quality of lives with the use of TKI and Avapritinib are a much better reflection in this complex disease spectrum.

Additional issues

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Single Technology Appraisal (STA)

Avapritinib for treating advanced systemic mastocytosis [ID3770]

EAG addendum: review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence data have been [redacted].

Table of Contents

Table of Tables

Table of Figures

1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to the key issues raised in the EAR, which were discussed at technical engagement (TE).

Please note that the EAG has had very limited time to critique the company's updated analyses, which equates to almost a new company submission (CS) presented as an addendum to the company's technical engagement response document. The EAG has focused on the impact of the updated data on the company's revised base case results.

The technical engagement covered 11 key issues, including the limitations of the data presented in the company's original submission that was primarily based on the September 2022 data cut-off of the ongoing PATHFINDER study. In response to EAG points for clarification, the company stated that an additional data cut-off was available (September 2023) and further details and updated analyses would be provided "at a later date". However, none of the key analyses were updated with the September 2023 data prior to technical engagement. The company's response to technical engagement includes a 94-page addendum with updated analyses from:

- PATHFINDER (15 September 2023 data cut-off, 200 mg starting dose)
- Pooled PATHFINDER and EXPLORER (15 September 2023 data cut-off for PATHFINDER and 19 January 2023 data cut-off for EXPLORER, 200 mg starting dose).

The updated pooled PATHFINDER and EXPLORER 2023 data, with the inverse probability of treatment weighting (IPTW) ECS analysis based on the updated data, is used in the company's economic analyses to provide a revised company base case.

The company's response to technical engagement indicates that they accept the EAG's judgement on issues 1, 5 and 8. Table 1 summarises the issues and whether the EAG considers them resolved, unresolved, and their remaining uncertainty. The EAG critique to the company's response to the issues identified in the EAR and the company's updated analyses is presented in Section 2. A summary of the company's changes to the modelled assumptions is presented in Section 3. The cost-effectiveness results of the company's updated base case are presented in Section 4.

Table 1 Summary of the key issues

Issue		Resolved?
1	Lack of clarity of what constitutes "best available therapy" at second or subsequent lines	Yes
2	Separation of the population by treatment line	No
3	Limitations of the effectiveness evidence	Partially resolved
4	Limitations of the indirect treatment comparisons	Partially resolved
5	Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Yes
6	Immaturity of the overall survival data used in the extrapolations	No (OS data remains immature and uncertain)
7	Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS	Partially resolved with more mature PFS data
8	Source of evidence used to inform time on treatment in the model	Yes
9	Uncertain duration of treatment benefit for avapritinib	No
10	Exclusion of subsequent therapy costs	No
11	Uncertainty in the progression-free and progressive disease health state utility values	No (PD utility value remains uncertain)

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 *Issue 1: Lack of clarity of what constitutes "best available therapy" at second or subsequent lines*

2.1.1 Background

In the company's original base case, best available therapy (BAT) was included as a comparator at second or subsequent lines (2L+) of therapy. However, BAT consisted of a range of off-label therapies including imatinib, interferon alpha and other off-label therapies not included in the NICE scope. It also included midostaurin, which is typically given at first line (1L) and assessed separately by the company as a comparator at 1L only. The EAG requested that midostaurin be excluded from the comparison of avapritinib with BAT at 2L+ because approximately [redacted] of patients in the 2L+ population in PATHFINDER had received prior midostaurin, which may have had an impact on survival outcomes for avapritinib at 2L. The EAG requested clear evidence on what therapies are given in the NHS after 1L midostaurin and the proportion of patients receiving midostaurin at 2L+.

2.1.2 Company's response

The company addressed the EAG's concerns regarding BAT at 2L+ by removing it as a comparator from the company's updated base case analyses. The company also indicates that the comparison of

avapritinib with cladribine at 2L+ is now less uncertain using the pooled PATHFINDER and EXPLORER 2023 data and, therefore, there is less need to consider the BAT comparator as a proxy for cladribine at 2L+. The company considers the following comparisons in the company's revised base case:

- avapritinib versus midostaurin at 1L
- avapritinib versus cladribine at 2L+

2.1.3 EAG's response

The EAG agrees with the removal of the comparator BAT (as a proxy for cladribine) at 2L+. However, the EAG does not fully agree that it is necessary to separate the population by treatment line (see Issue 2).

In summary, the EAG considers Issue 1 resolved.

2.2 *Issue 2: Separation of the population by treatment line*

2.2.1 Background

The EAG considered there to be limited justification for the separation of the population by treatment line, when the NICE recommendation for midostaurin is not restricted to the 1L population, and because cladribine is most likely used as a subsequent treatment after either midostaurin or avapritinib.

2.2.2 Company's response

The company holds their original position that the population should be separated by treatment line because midostaurin is well-defined in the treatment pathway as a 1L option and cladribine is the most appropriate comparator in the 2L+ setting. The company have not presented new analyses to address issue 2.

2.2.3 EAG's response

The EAG believes that there is merit in assessing the cost-effectiveness of avapritinib compared with midostaurin in the overall population, i.e., not separated by line of treatment, because (i) the [redacted]; and (ii) in TA728, the NICE recommendation for midostaurin is not restricted to the 1L population setting only. Whilst the EAG acknowledges that it is clear that the majority of patients are likely to be treated at first line with midostaurin in the NHS, there are some patients (mainly historic) who will receive midostaurin as a second line treatment; which was reflected in the company's original comparison with BAT from the ECS, where BAT consisted of a mixture of therapies, including [redacted]

of patients receiving midostaurin. The EAG still believes that there is merit in assessing the cost-effectiveness of avapritinib compared with midostaurin in the overall population, i.e., not separated by line of treatment. This would involve using data from the entire ECS for midostaurin, who had received ≥1 line of systemic therapy (not necessarily as 1L) for AdvSM and data for avapritinib from PATHFINDER 2023 (and/or combined with EXPLORER 200 mg OD 2023), with an adjustment made to balance for differences in treatment lines using propensity weights; this also avoids discarding data by prior use of systemic therapies, which is necessary when splitting the data by treatment line.

In summary, the EAG considers Issue 2 unresolved.

2.3 Issue 3: Limitations of the effectiveness evidence

2.3.1 Background

Data on the efficacy and safety of avapritinib is based on two single-arm studies. In the original CS, the company presented data from the September 2022 data cut-off for PATHFINDER, as well as a pooled analysis of PATHFINDER and EXPLORER from April 2021 and June 2020. The EAG deemed the lack of long-term data to be a key issue in the original CS due to data immaturity, and that later data-cuts would help to reduce some of the uncertainty in the overall and progression-free survival.

2.3.2 Company's response

The company agreed that the clinical evidence presented in the CS was uncertain and immature. Alongside the TE response, the company provide updated effectiveness data from the data cut-offs for PATHFINDER (September 2023 data-cut) and pooled PATHFINDER and EXPLORER (September and January 2023 data-cut off respectively) studies.

Response rates in the PATHFINDER study (September 2023 data cut-off) were consistent with the previous data cut-offs. The response rates in the pooled PATHFINDER and EXPLORER population showed similar, yet slightly lower overall response rate (see company's additional evidence addendum, Table 4).

In the most recent data cut-off for PATHFINDER, median PFS is reached for 1L population, and for the total population (summarised in Table 2). In the pooled PATHFINDER and EXPLORER study, median PFS is reached for the total population, and for the 1L and 2L+ populations (Table 5 of the company's additional evidence addendum). For overall survival, median OS was reached in the pooled PATHFINDER and EXPLORER 2L+ population only.

2.3.3 EAG's response

The EAG agree with the company that response rates from the updated PATHFINDER and pooled PATHFINDER and EXPLORER are [redacted].

The results from the PATHFINDER and the pooled PATHFINDER and EXPLORER studies are [redacted] between the studies (see EAG response to Issues 6 and 7 below). The EAG noted that there are [redacted] in PFS estimates from the PATHFINDER 2022 and 2023 data cut-offs (Table 2). [redacted]. This results in a [redacted] PFS estimate from the updated 2023 data cut-off. The implications of this on the cost-effectiveness of avapritinib are discussed further in Section 2.6 and 2.7 (key issues 6-7).

Table 2. Comparison between PFS in PATHFINDER 2022 and 2023 data cut-offs

	PATHFINDER 2022 data cut-off			PATHFINDER 2023 data cut-off		
	1L	2L+	All	1L	2L+	All
Progression-free survival						
Events, n (%)	4 (13.3)	16 (31.4)	20 (24.7)	[redacted]	[redacted]	[redacted]
Censors, n (%)	26 (86.7)	35 (68.6)	61 (75.3)	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimate						
Median PFS	39.4 (39.4, NE)	NE (30.2, NE)	NE (39.4, NE)	[redacted]	[redacted]	[redacted]
12 months (95% CI)	93.0 (83.6, 100.0)	77.9 (66.3, 89.5)	83.5 (75.2, 91.7)	[redacted]	[redacted]	[redacted]
24 months (95% CI)	89.4 (78.1, 100.0)	68.8 (55.5, 82.0)	76.5 (66.9, 86.0)	[redacted]	[redacted]	[redacted]
36 months (95% CI)	89.4 (78.1, 100.0)	64.2 (49.1, 79.3)	73.4 (62.5, 84.3)	[redacted]	[redacted]	[redacted]

Data obtained from original company submission (Table 12) for PATHFINDER 2022, and company's additional evidence addendum for PATHFINDER 2023 (Table 5).

The EAG noted some errors or discrepancies in the reporting of the updated results including:

- Number of patients discontinuing avapritinib due to adverse events (Table 2 and Table 9 of the TE additional evidence addendum)

- Number of deaths in the 2L+ population in the pooled PATHFINDER and EXPLORER trials (Table 2 and Table 17).
- Discordance in reporting of the company's approach to including region in the adjustment in the IPTW in the 2L population between the TE response and additional evidence addendum.

The EAG also note that analyses for a pooled PATHFINDER and EXPLORER population using data from the most recent EXPLORER data cut-off (April 2023), which was used to inform some of the responses to clarification questions previously, have not been provided.

The EAG consider that the updated data cut-offs have reduced uncertainty in the PFS estimates, but not in OS estimates. However, the lack of comparative clinical trials of avapritinib versus midostaurin or cladribine is still a limitation.

In summary, the EAG considers issue 3 to be partially resolved.

2.4 Issue 4: Limitations of the indirect treatment comparisons

2.4.1 Background

In the original CS, the company presented a number of indirect treatment comparisons including an inverse probability of treatment weighting (IPTW) analysis using an external control study (ECS) which includes real-world data on BAT including midostaurin and cladribine. This was used to inform the company's base case analysis in the economic model. The IPTW analyses used PATHFINDER data from September 2022, and pooled PATHFINDER and EXPLORER data from April 2021. The company also conducted a matching-adjusted indirect comparison (MAIC) analysis using individual participant data from the PATHFINDER and EXPLORER studies, alongside aggregate data from the two phase 2 studies of midostaurin in patients with AdvSM (D2201 and A2213). The MAIC analyses used PATHFINDER data from April 2021, and pooled PATHFINDER and EXPLORER data from April 2021 and May/June 2020.

The EAG's main critique at the point of submission was that the IPTW and MAIC analyses were based on an early data cut-off and were therefore not providing the most up-to-date evidence on the efficacy of avapritinib.

The EAG considered the IPTW to be the most appropriate indirect treatment comparison but had concerns with the adjustment for baseline characteristics in the IPTW, especially around the limited detail on the methods of adjustment, the lack of adjustment for key prognostic variables including C-findings, bone marrow mast-cell burden and *KIT D816V* mutation status, and the potential over-adjustment for variables that may not be prognostic (e.g., region).

At points for clarification, the EAG requested additional details on the methods of adjustment in the IPTW, the majority of which have now been provided in the additional evidence addendum for the new data cut-offs. This included standardised differences before and after adjustment (Table 13-15 of the additional evidence addendum, and for DOT at 1L in an additional data on file[1]), a summary of the truncated weights (Table 12 of the additional evidence addendum), and the propensity score distributions before and after weighting for each analysis (Appendix A of the additional evidence addendum).

2.4.2 Company's response

The company agrees with the EAG that the IPTW analysis is the most appropriate, and provided an updated IPTW analysis using the pooled PATHFINDER (Sept 2023 data cut-off, 200mg starting dose) and EXPLORER (Jan 2023 data cut-off, 200mg starting dose) safety population and the ECS, which has not been updated since the original company submission.

The company argued that "region" was an important factor to adjust for owing to potential differences in treatment between study sites. However, they conducted a sensitivity analysis to illustrate the impact of including region in the IPTW in the 1L setting. When region was removed from the IPTW, the adjusted HR (aHR) was [redacted], compared to [redacted] when region was included in the IPTW weighting. [redacted] The EAG note that in the TE response, the company say that region is not adjusted for in the 2L+ population analyses, but the tables in the additional evidence addendum suggests otherwise (Tables 14-15 of the company addendum), so it is unclear whether region was considered in the IPTW analyses.

The company provides justification for choosing variables for adjustment – and provide details as to why C-findings, KIT D816V and bone marrow mast-cell burden were not included. Namely, data on C-findings and bone marrow mast-cell burden, may not have been collected in clinical practice and were therefore, not available for adjustment. *KIT D816V* mutation status was available, but as >90% of the patients in both the ECS and the pooled PATHFINDER and EXPLORER population were *KIT D816V* positive, the association between treatment allocation and mutation status would be weak.

2.4.3 EAG's response

Following the updated IPTW analysis using the latest data cut-offs, as well as additional evidence on the baseline characteristic adjustment including distribution of propensity scores and additional details on IPTW weights, the EAG consider some of the uncertainties associated with the IPTW to be resolved. This includes details on the methods of baseline adjustment, which shows the improvement

in the overlap of the propensity scores before and after adjustment and an effective sample size that is similar to the unadjusted population. The EAG would have also liked to see the distribution of weights (in addition to the propensity scores) to determine the number of patients who were significantly down or up weighted.

Despite this, there are key prognostic variables that may lead to residual bias in the baseline characteristics, meaning the company's analysis does not meet one of the key assumptions in IPTW methods (no unmeasured confounders). While the EAG acknowledge that the ECS may not have collected data on C-findings and bone marrow mast-cell burden and therefore, could not be controlled for in the adjustment, it does not mean that they are not potentially prognostic and could impact the direction or magnitude of effect. As the number of C-findings and the bone marrow mast cell burden are unknown in the ECS, it is difficult to determine the extent to which they differ between the comparator and avapritinib populations and how that may impact the results. The EAG agree with the company that *KIT 816V* mutation status is highly prevalent in both groups and that association between treatment allocation and mutation status is likely to be weak. However, the company's MAIC did adjust for *KIT 816V* mutation status as it was deemed 'potentially prognostic', so lack of adjustment in the IPTW is still a limitation.

As described in Section 3.6 of the EAR, the EAG still consider it difficult to ascertain the reliability of the findings of the ITCs, as results from the IPTW and MAIC are not comparable since they do not present analyses for the same populations (based on treatment line and dose). Therefore, the EAG still consider there to be uncertainties with the IPTW, owing to unmeasured confounding variables, and the lack of plausible comparisons between the IPTW and the MAIC for patients receiving avapritinib at 200mg in the NHS.

In summary, the EAG consider Issue 4 to be partially resolved.

2.5 *Issue 5: Lack of consistency in the source of evidence used to inform the different survival parameters in the model*

2.5.1 Background

The EAG noted that there was a lack of consistency in the sources of data used to inform the different survival parameters in the model. The company used the PATHFINDER safety population for OS for avapritinib, adjusted for IPTW, but used the Response Assessment Committee response-evaluable (RAC-RE) population unweighted analysis for PFS for avapritinib. More importantly, however, the time on treatment (TOT) curve for avapritinib was not informed by PATHFINDER and, therefore, it was not consistent with the PFS and OS outcomes used in the model. Furthermore, the approach used to determine the probability of moving to the progressive disease health state, via the PFS and OS

curves, differed for avapritinib and the comparators, where the TOT curve was used as a proxy for PFS for the comparators but not for avapritinib. This mismatch of different sources of evidence to inform three inter-related parameters in the model (PFS, TOT and OS) was a major concern because it created inconsistencies in the data used.

2.5.2 Company's response

The company acknowledged the EAG's concerns. The economic analyses were updated with pooled PATHFINDER and EXPLORER 2023 data such that the following data sources are used in the company's updated base case:

- OS – pooled PATHFINDER/EXPLORER 2023 safety population, adjusted for IPTW from the ECS;
- PFS – pooled PATHFINDER/EXPLORER 2023 RAC-RE population for avapritinib and TOT from ECS IPTW as a proxy for PFS for comparators;
- TOT – pooled PATHFINDER/EXPLORER 2023 safety population, adjusted for IPTW from the ECS.

2.5.3 EAG's response

The company have addressed the EAG's concerns. The company's economic analyses have substantially changed during technical engagement by using the updated pooled PATHFINDER and EXPLORER 2023 data for treatment effectiveness in the model and the updated source of evidence used to inform TOT and PFS. The impact of these changes is discussed under the relevant issues below and assessed in relation to the company's updated base case results in Section 4.

In summary, the EAG considers Issue 5 resolved.

2.6 *Issue 6: Immaturity of the overall survival data used in the extrapolations*

2.6.1 Background

The EAG expressed a key concern that the OS data used in the company's base case analysis from PATHFINDER September 2022 data cut-off is immature, with median OS not reached in either the safety or RAC-RE populations. The immature OS data was extrapolated beyond the limited follow-up of PATHFINDER using different parametric distributions, which led to very different long-term survival outcomes. The EAG also noted that the extent to which the different parametric extrapolations had an impact on cost-effectiveness was dependent on the duration of treatment benefit for avapritinib, which was assumed to be 5 years in the company's original model.

2.6.2 Company's response

The company's updated pooled PATHFINDER/EXPLORER 2023 data for OS from the safety population provides an additional 10 months of follow up compared with PATHFINDER 2022; however, median OS has not yet been reached in the updated data cut-off in PATHFINDER 2023.

2.6.3 EAG's response

The company did not discuss the impact of including EXPLORER data on survival outcomes. In order to understand the impact of using the updated pooled PATHFINDER/EXPLORER 2023 data on OS compared to the PATHFINDER September 2022 data cut-off (original company base case analysis), the EAG first looked at a comparison of OS from PATHFINDER 2023 data (not pooled) with pooled PATHFINDER/EXPLORER 2023 with a view to assessing the impact of including EXPLORER data on the outcome of OS. Once the impact of EXPLORER data was assessed, then the EAG could consider the impact of pooled PATHFINDER/EXPLORER 2023 data vs. PATHFINDER September 2022 data on OS.

Figure 1 shows the Kaplan-Meier (K-M) curves for OS by prior systemic therapy for the inclusion of EXPLORER (pooled 2023 data) and exclusion of EXPLORER (not pooled, i.e., PATHFINDER 2023 without EXPLORER). The inclusion of EXPLORER data increases the sample size by [redacted] patients in the 1L setting (no prior systemic therapy) and [redacted] patients in the 2L+ setting (prior systemic therapy). The additional data from EXPLORER [redacted], either in the 1L or 2L+ setting, with OS [redacted] in EXPLORER than PATHFINDER in those with no prior systemic therapy. The EAG is reasonably satisfied that [redacted] for the outcome of OS.

Figure 1 Comparison of OS from pooled PATHFINDER/EXPLORER 2023 data and PATHFINDER 2023 data (not pooled).

[redacted]

The EAG then compared OS from pooled PATHFINDER/EXPLORER 2023 data vs. PATHFINDER September 2022 data (Figure 2). The additional 10 months of follow-up data from PATHFINDER results in [redacted] OS in the 1L setting. In the original PATHFINDER 2022 data, the OS K-M estimate for patients who had not received prior systemic therapy at 24 months was 88.5%, while in the pooled PATHFINDER/EXPLORER 2023 data the corresponding estimate at 24 months is [redacted]%, resulting from [redacted] OS in both EXPLORER 2023 and PATHFINDER 2023. In patients who had received prior systemic therapy, the K-M estimate for OS at 24 months was 73.6% in the original PATHFINDER 2022 data, while the corresponding estimate for OS at 24 months is [redacted]% in the pooled PATHFINDER/EXPLORER 2023 data.

Figure 2 Comparison of OS from pooled PATHFINDER/EXPLORER 2023 data (updated base case analysis) and PATHFINDER 2022 data (original base case analysis).

The EAG notes that the company's updated base case OS extrapolation predicts [redacted]% and [redacted]% of patients to be alive at 24 months for the 1L and 2L+ populations, respectively, which are [redacted] than the corresponding K-M estimates of [redacted]% and [redacted]% from the pooled PATHFINDER/EXPLORER 2023 data. The EAG also notes that the extrapolated OS data beyond the follow-up of PATHFINDER/EXPLORER 2023 using different parametric distributions leads to very different long-term survival outcomes (Figure 3 for 1L setting). The company have selected the generalised gamma in the 1L setting for its base case analysis based on lowest AIC/BIC criterion. However, as noted in the EAR the extent to which the different parametric extrapolations have an impact on the cost-effectiveness results is also dependent on the duration of treatment benefit assumed for avapritinib, which the company has increased from 5 years to 7.5 years in their updated base case (see Issue 9).

Figure 3 OS Kaplan-Meier curve from pooled PATHFINDER/EXPLORER 2023 and fitted parametric distributions for avapritinib in the 1L setting (generalised gamma [G.Gamma] used in company's updated base case analysis).

The EAG does not consider that the updated pooled PATHFINDER/EXPLORER 2023 data has significantly reduced uncertainty in the OS estimates. The EAG remains concerned about the immaturity of the OS data, which has not yet reached median OS in either the 1L or 2L+ settings.

In summary, the EAG considers Issue 6 unresolved.

2.7 *Issue 7: Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS*

2.7.1 Background

PFS was not available from the ECS to enable an IPTW comparison with PATHFINDER. Therefore, the company used the comparator's TOT curve as a proxy for the comparator's PFS curve, but not for avapritinib. The EAG expressed a concern that the PFS data for avapritinib from the RAC-RE population (unweighted analysis) of PATHFINDER was inconsistent with the OS data from the safety population (IPTW sample) of PATHFINDER used in the company's base case analysis because the PFS curve for avapritinib was equal to the OS curve for avapritinib in the first 5 years of treatment, i.e., no proportion of the cohort in the avapritinib arm entered the progressive disease health state. This assumption was required in the model because the extrapolated PFS data from the RAC-RE population (unweighted analysis) was greater than the extrapolated OS data from the safety population (weighted analysis) in the first 5 years, so the PFS curve was capped at the OS curve. The EAG also considered this assumption to be unreasonable in light of the TOT curve used in the model for avapritinib, which has a median duration of treatment of 16.56 months. The EAG concluded that the PFS data from the unweighted RAC-RE population of PATHFINDER was unfit for purpose and, therefore, the only reasonable approximation for PFS was to use the TOT curve as a proxy for PFS in

both the avapritinib and comparator arms in the model, in order to ensure consistency with OS and consistency across treatment arms.

2.7.2 Company's response

The company indicates that ECS IPTW could not provide comparative data on PFS because the outcome was not recorded in the retrospective real-world cohort and, even where time to progressive disease could be accurately determined, the response to treatment, including progression criteria, used in different centres were not consistent with those used in PATHFINDER and EXPLORER.

The company provides updated PFS estimates from pooled PATHFINDER and EXPLORER 2023 in the RAC-RE population for both the 1L and 2L+ patients, which have reached median PFS of [redacted] months and [redacted] months, respectively, which the company believes now addresses the EAG's concerns about the immaturity of the PFS curves and resolves inconsistencies with OS data from the safety population. The company uses the PFS estimates from pooled PATHFINDER/EXPLORER 2023 (unweighted analysis) for avapritinib in its updated base case analysis. A number of alternative scenarios are also presented (see company's response to technical engagement for details of the scenarios), including the EAG's original preferred assumption of using IPTW-adjusted TOT as a proxy for PFS for avapritinib.

2.7.3 EAG's response

The EAG acknowledges the lack of PFS data from the ECS for the comparators. Therefore, the only available PFS data is from PATHFINDER and EXPLORER (unweighted analysis) for avapritinib. In order to assess the consistency of EXPLORER 2023 PFS with PATHFINDER 2023 PFS from the RAC-RE population, the EAG first looked at a comparison of PFS from PATHFINDER 2023 data (not pooled) with pooled PATHFINDER/EXPLORER 2023. Figure 4 shows the K-M curves for PFS by prior systemic therapy for the inclusion of EXPLORER (pooled 2023 data) and exclusion of EXPLORER (PATHFINDER 2023). The inclusion of EXPLORER increases the sample size by [redacted] patients in the 1L setting and [redacted] patients in the 2L+ setting. The additional data from EXPLORER [redacted], either in the 1L or 2L+ setting, with the PFS curve for EXPLORER 2023 indicating a [redacted] than PATHFINDER 2023 in those with no prior systemic therapy. The EAG is reasonably satisfied that the findings from [redacted] for the outcome of PFS.

Figure 4 Comparison of PFS from pooled PATHFINDER/EXPLORER 2023 data and PATHFINDER 2023 data (not pooled).

The EAG then compared PFS from pooled PATHFINDER/EXPLORER 2023 data with PATHFINDER September 2022 data, used in the company's original base case (Figure 5). The additional 10 months of follow-up data from PATHFINDER results in PFS in the 1L setting. In the original PATHFINDER 2022 data, 75.3% of patients were censored from the analysis, while only 24.7% had died or progressed in disease. Figure 5 suggests , particularly for patients who did not receive prior systemic therapy.

Figure 5 Comparison of PFS from pooled PATHFINDER/EXPLORER 2023 data (updated base case analysis) and PATHFINDER 2022 data (original base case analysis).

The EAG considers that the pooled PATHFINDER/EXPLORER 2023 PFS data has alleviated concern about the immaturity of the PFS data for avapritinib because median PFS has been reached in both the 1L and 2L+ settings. However, the model still relies on PFS data from the 1L and 2L+ RAC-RE analysis for avapritinib, which is unweighted (i.e., no IPTW comparison with data from the ECS). In the company's original base case, PFS was set equal to OS for the first 5 years in the model. This is no longer the case in the company's updated base case, where pooled PATHFINDER/EXPLORER 2023 PFS (unweighted) is [redacted] than OS from month 24 onwards (Figure 6). The PFS data for avapritinib is extrapolated beyond the follow-up of the RAC-RE population of PATHFINDER/EXPLORER 2023 using different parametric distributions, which lead to different estimates of long-term PFS (Figure 7). The company has selected the exponential distribution for its base case analysis in the 1L setting based on lowest AIC/BIC criterion. As noted for OS, the extent to which the different parametric extrapolations have an impact on the cost-effectiveness results is also dependent on the duration of treatment benefit assumed for avapritinib, which is 7.5 years (90 months) in the company's updated base case analysis (see issue 9).

In the EAR, the EAG concluded that the only reasonable approximation for PFS was to use the TOT curve as a proxy for PFS for both avapritinib and its comparators. The EAG considers that this argument no longer holds because the updated PATHFINDER/EXPLORER 2023 PFS data is now consistent with the OS data used in the model (i.e., K-M PFS is no longer greater than K-M OS). However, there remains uncertainty about long-term PFS and the duration of avapritinib benefit.

In summary, the EAG considers Issue 7 to be partially resolved.

Figure 6 Kaplan-Meier curves for PFS from the unweighted RAC-RE population of PATHFINDER/EXPLORER 2023 and OS from the weighted safety population of PATHFINDER/EXPLORER 2023 for avapritinib in the 1L setting.

Figure 7 PFS Kaplan-Meier curve from pooled PATHFINDER/EXPLORER 2023 and fitted parametric distributions for avapritinib in the 1L setting (exponential used in company's updated base case analysis).

2.8 *Issue 8: Source of evidence used to inform time on treatment in the model*

2.8.1 Background

In the company's original base case analysis, TOT for avapritinib was sourced from a small cohort of 13 patients treated with avapritinib in the UK as part of the Compassionate Use Program (CUP). The EAG considered the choice of TOT curve for avapritinib as a major limitation of the company's base case analysis because: (i) it was not consistent with the OS outcomes used in the model; (ii) it was based on a very small cohort of 13 patients and only 9 of these patients received the starting dose of avapritinib 200 mg OD; (iii) the data was not separated by treatment line as required by the model because 10 out of the 13 patients received avapritinib as a first line regime; (iv) KM data for duration of therapy in CUP was not available and therefore the company applied a simple exponential distribution to the median duration of treatment to derive a parametric curve over time; and, importantly, (v) an IPTW ITC of avapritinib and the comparators was not used for the TOT curves in the model. Moreover, the EAG noted that TOT was a critical parameter in the model because it determines the duration of therapy, with associated drug acquisition costs, and it provides a proxy for PFS for the comparators, which drives treatment costs and duration of health-related quality of life benefits associated with PFS compared to PD.

2.8.2 Company's response

The company has revised its base case analysis to use the updated ECS IPTW analysis from pooled PATHFINDER/EXPLORER 2023 to inform TOT for avapritinib and the IPTW sample from ECS for comparator TOT, which aligns with the OS outcomes used in the updated model, EAG preferred

assumptions and feedback from consultant haematologists, while TOT data from the CUP (N=13) was explored in a scenario analysis.

2.8.3 EAG's response

The EAG considers the revised approach used by the company to be appropriate, where the K-M data for duration of treatment from the pooled PATHFINDER/EXPLORER 2023 safety population (to match that used for OS) is extrapolated over time, adjusted for IPTW, and the IPTW sample from the ECS used for TOT for the comparators. The EAG considers the K-M data for TOT to be relatively mature, with less uncertainty in the extrapolated fitted distributions (see Figures 19-22 of the addendum to the company's response to technical engagement).

The EAG notes that the median TOT for avapritinib from the pooled PATHFINDER/EXPLORER 2023 IPTW analysis in the 1L setting of [redacted] months is [redacted] than the PATHFINDER 2022 IPTW analysis of [redacted] months. The reasons for the [redacted] TOT are unclear, but the EAG notes that it is consistent with [redacted] PFS in the 1L setting for the pooled analysis compared to the original PATHFINDER 2022 data cut.

In summary, the EAG considers Issue 8 to be resolved.

2.9 *Issue 9: Uncertain duration of treatment benefit for avapritinib*

2.9.1 Background

The duration of treatment benefit for avapritinib was assumed to be 5 years in the company's original base case analysis based on the rate of duration of response in PATHFINDER 2022 of 70.5% (95% CI, 43.5 to 97.4%) at 42 months in the RAC-RE population for all AdvSM patients. The EAG considered the assumption of a 5-year treatment benefit for avapritinib to be reasonable in the 1L population but acknowledged that this could potentially be pessimistic when using the TOT curves from the parameterised IPTW outcomes from PATHFINDER 2022 for avapritinib because approximately [redacted]% of patients were still on treatment at 5 years. However, the EAG also noted that it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes assumed in the model; for example, if the extrapolation of OS based on immature data is highly optimistic, then an appropriate cap on the duration of treatment benefit is required.

2.9.2 Company's response

The company acknowledged the EAG's concern and supported the view that it is not possible to consider the duration of treatment benefit in isolation of the survival outcomes. In their updated base case, the company noted that using the pooled PATHFINDER/EXPLORER 2023 ECS IPTW analysis to inform TOT resulted in a greater proportion of patients remaining on treatment at 7.5 years ([redacted]%

vs. [redacted]% in the company's original base case in the 1L setting and [redacted]% vs. [redacted]% in the 2L+ setting). Therefore, the company have updated their treatment benefit assumption of 5 years to 7.5 years to reflect the longer treatment duration, which the company states is in line with expectations from UK consultant haematologists.

2.9.3 EAG's response

Under the assumption that more sustained disease response is achieved while patients continue to receive avapritinib, the EAG considers the company's revised treatment benefit of 7.5 years to be reasonable in light of the longer duration on treatment in the updated pooled PATHFINDER/EXPLORER 2023 ECS IPTW analysis. However, as noted previously in the EAR (Section 4.2.6.2), the duration of treatment benefit should not be considered in isolation of the survival outcomes. EAG Scenarios in Section 4 demonstrate the interplay between the duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered; the results show that [redacted] are highly sensitive to these assumptions.

In summary, the EAG considers there to be uncertainty about the duration of treatment benefit for avapritinib relative to its comparators and, therefore, Issue 9 remains unresolved.

2.10 Issue 10: Exclusion of subsequent therapy costs

2.10.1 Background

The impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment was not considered in the company's original base case analysis in the 1L or 2L+ settings. The EAG expressed concern that there may be potential confounding of subsequent treatment effects on survival outcomes reported in PATHFINDER for avapritinib, but that the costs (and utility values) associated with the use of subsequent therapies were excluded from the model, particularly, for the proportion of the cohort who received allo-HSCT.

2.10.2 Company's response

The company indicated that are no data on subsequent treatment use and post-progression survival outcomes to inform the model. The company also states that feedback received from UK consultant haematologists suggests that subsequent treatment received after avapritinib 1L would be cladribine ([redacted]) and AML like treatment ([redacted]). The company conducted a scenario "informed by KOL feedback on the impact of subsequent treatment costs on the model" but no details are provided.

2.10.3 EAG's response

The EAG is concerned that there may be potential confounding of subsequent treatment effects on survival outcomes reported in the updated pooled PATHFINDER/EXPLORER 2023 data for the proportion of the cohort who received allo-HSCT post-avapritinib discontinuation; however, no information on treatments used post-avapritinib discontinuation is reported.

In summary, the EAG considers Issue 10 unresolved.

2.11 *Issue 11: Uncertainty in the progression-free and progressive disease health state utility values*

2.11.1 Background

The EAG noted uncertainty in the utility values for the PF and PD health states. The utility data from PATHFINDER September 2022 data cut-off had a limited number of observations at each time point to inform the mapped utility value associated with PF in the 1L and 2L+ populations. The EAG also had a number of concerns about the PD/PF utility ratio used in the company's analysis to derive a utility value for PD.

2.11.2 Company's response

The company have provided updated health state utility values using pooled PATHFINDER/EXPLORER 2023 data in Table 5 of the company's response to technical engagement.

2.11.3 EAG's response

The company have provided no details on the number of additional observations used to inform the updated PF health state utility value. The concerns raised by the EAG in Section 4.2.8.2 of the EAR about the PD/PF utility ratio used in the company's original analysis remain as the company have used the same methodology to derive the PD health state utility value used in their revised base case.

In summary, the EAG considers Issue 11 unresolved.

3 UPDATED MODELLING ASSUMPTIONS

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The following EAG-preferred assumptions are incorporated within the company's revised model:

- Updated outcomes from the most recent data cut-off from the ongoing PATHFINDER study: the company have provided updated outcomes from pooled PATHFINDER September 2023 and EXPLORER January 2023 data cut-offs.

- Time on treatment based on ECS IPTW analysis from the most recent data cut-off from PATHFINDER (pooled PATHFINDER/EXPLORER 2023) for avapritinib.

- Time on treatment based on ECS IPTW analysis for the comparators using the most recent data cut-off from PATHFINDER (pooled PATHFINDER/EXPLORER 2023).

In addition, the EAG agrees with the following assumptions incorporated in the company's revised model (where data were previously immature for EAG base case):

- PFS based on the most recent data cut-off from PATHFINDER (pooled PATHFINDER/EXPLORER 2023) for avapritinib.

- Duration of treatment benefit of 7.5 years for avapritinib, in light of the longer duration of treatment from the updated pooled PATHFINDER/EXPLORER 2023; however, the EAG notes that the duration of relative treatment benefit remains uncertain, and it should not be considered in isolation of the size of the treatment effect.

- Updated health state utility values based on pooled PATHFINDER/EXPLORER 2023.

Furthermore, the company have excluded the comparison of avapritinib with 2L+ BAT.

4 RESULTS

4.1 Company's updated cost-effectiveness results

Table 3 and Table 4 show the cost-effectiveness results for the company's updated base case analysis following technical engagement for the comparison of avapritinib with midostaurin at 1L and cladribine at 2L+, respectively. These results are inclusive of the approved PAS discount for avapritinib but are exclusive of the confidential cPAS discount for midostaurin. The corresponding cost-effectiveness results with cPAS discount for midostaurin is provided in a confidential appendix separate to this document.

Table 3 Company's updated base-case results following technical engagement for the comparison of avapritinib with 1L midostaurin (as reported in company's response to TE)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Avapritinib	[redacted]	7.46	5.01	[redacted]	4.30	2.95	[redacted]
Midostaurin	[redacted]	3.16	2.06				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 4 Company's updated base-case results following technical engagement for the comparison of avapritinib with 2L+ cladribine (as reported in company's response to TE)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Avapritinib	[redacted]	5.12	3.19	[redacted]	2.34	1.77	[redacted]
Cladribine	[redacted]	2.79	1.42				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

However, the EAG noted that the company's updated base case results did not align with the summary of base case inputs in Table 42 and Table 43 for the 1L and 2L+ comparisons, respectively, of the addendum to the company's response to technical engagement. The EAG noted the following discrepancies:

- The results reported in Table 3 are based on a generalised gamma distribution for the extrapolation of PFS for avapritinib at 1L, whereas Table 42 summarising the base case inputs suggests an exponential distribution for PFS extrapolation; and
- The results reported in Table 4 are based on an exponential distribution for the extrapolation of OS for cladribine at 2L+, whereas Table 43 summarising the base case inputs suggests a log-normal distribution for OS extrapolation.

The EAG believes that the company's reporting of base case results in Table 3 and Table 4 are in error, where the extrapolations for PFS in the 1L setting, and OS in the 2L+ setting, have not been updated as intended by the company. The EAG-corrected cost-effectiveness results for the company's updated base case analysis for the comparisons of avapritinib with 1L midostaurin and 2L+ cladribine are presented in Table 5 and Table 6, respectively.

Table 5 Corrected company's updated base-case results following technical engagement for the comparison of avapritinib with 1L midostaurin

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Avapritinib	[redacted]	7.46	4.92	[redacted]	4.30	2.87	[redacted]
Midostaurin	[redacted]	3.16	2.06				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 6 Corrected company's updated base-case results following technical engagement for the comparison of avapritinib with 2L+ cladribine

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Avapritinib	[redacted]	6.66	3.89	[redacted]	2.54	1.86	[redacted]
Cladribine	[redacted]	4.12	2.03				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The updated deterministic ICER for avapritinib relative to midostaurin at 1L [redacted]. The updated deterministic ICER for avapritinib vs cladribine at 2L+ is [redacted], [redacted] from the company's original base case of [redacted].

Figure 8 and Figure 9 show the survival curves used in the company's updated base case analysis following technical engagement vs. company's original analysis for the comparisons with midostaurin at 1L, and cladribine at 2L+, respectively. The main differences lie in the PFS curves, time on treatment, and duration of treatment benefit.

The QALYs for avapritinib at 1L increase from 4.31 in the company's original base case analysis to 4.92 in the company's updated base case following technical engagement. This increase is the result of the extension of the longer duration of treatment effect for avapritinib of 7.5 years. The updated QALYs for midostaurin at 1L has minimal difference compared to the original analysis (2.03 vs 2.06, respectively). The total cost of avapritinib at 1L [redacted] from [redacted] in the updated analysis as a result of the longer duration on treatment for avapritinib based on the ECS IPTW analysis from pooled PATHFINDER/ EXPLORER 2023 rather than CUP. This approach is in line with the EAG's preferred modelling approach in the EAR. Similarly, the total cost of midostaurin at 1L [redacted] from [redacted] as a result of using a longer duration of treatment from the updated ECS IPTW analysis for midostaurin.

Figure 8 Survival curves used in the company's base case analysis for the comparison of avapritinib with 1L midostaurin in:

a. The original company base case

b. Updated company base case (EAG-corrected)

Figure 9 Survival curves used in the company's base case analysis for the comparison of avapritinib with 2L+ cladribine in:

a. The original company base case

b. Updated company base case (EAG-corrected)

For the 2L+ comparison, total QALYs for avapritinib increase from 2.50 in the company's original base case to 3.89 in the updated base case. This increase results from the extension of the duration of treatment effect for avapritinib from 5 years to 7.5 years, and the log-normal parametric extrapolation for OS of cladribine at 2L+ rather than exponential (i.e., after 7.5 years, the OS hazard rate for avapritinib is set equal to the OS hazard rate for cladribine, which is informed by the log-normal extrapolation in the company's updated base case). The total QALYs for cladribine at 2L+ in the updated analysis are also greater than the original analysis because of the switch to a log-normal distribution for the extrapolation of OS for cladribine. The total cost of avapritinib at 2L+ [redacted] from [redacted] as a result of using the updated time on treatment curve based on the ECS IPTW analysis from pooled PATHFINDER/ EXPLORER 2023 for avapritinib. The total cost of

cladribine at 2L+ [redacted] from [redacted] as a result of the updated ECS IPTW analysis for cladribine. This approach is in line with the EAG's preferred modelling approach in the EAR.

4.2 EAG preferred base case

The company's updated base case cost-effectiveness results (EAG-corrected) match the EAG's preferred set of assumptions. The EAG's base case is now the same as the company's updated base case results in Table 5 and Table 6.

The EAG has undertaken additional scenario analysis to assess the impact of alternative duration of treatment effect and the size of the treatment effect when different parametric survival extrapolations are considered (similar to the scenarios presented in Table 24 and Table 25 of the EAR). The corresponding cost-effectiveness results are shown in Table 7 and Table 8 for the comparison of avapritinib with midostaurin at 1L and cladribine at 2L+, respectively. The EAG notes that scenario 1 in Table 24 and Table 25 of the EAR have been included in the company's updated base case, while scenario 2 in the EAR is no longer appropriate in the light of the updated data.

Table 7 Cost-effectiveness results of EAG scenario - avapritinib vs 1L midostaurin

Scenario #	Name	Option	Costs (£)	QALYs	Inc. Costs (£)	Inc. QALYs	ICER, /QALY
	Company updated base case: EAG preferred base case	Avapritinib	[redacted]	4.92	[redacted]	2.87	[redacted]
		Midostaurin	[redacted]	2.06			
3a	Pessimistic OS extrapolation for avapritinib: exponential (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.74	[redacted]	2.68	[redacted]
		Midostaurin	[redacted]	2.06			
3b	Optimistic OS extrapolation for avapritinib: Gompertz (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.97	[redacted]	2.91	[redacted]
		Midostaurin	[redacted]	2.06			
3c	Pessimistic OS extrapolation for midostaurin: exponential (similar extrapolation to the company's base case) (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.97	[redacted]	2.91	[redacted]
		Midostaurin	[redacted]	2.06			
3d	Optimistic OS extrapolation for midostaurin: log normal (duration of TE of 7.5 years)	Avapritinib	[redacted]	5.76	[redacted]	3.48	[redacted]
		Midostaurin	[redacted]	2.28			
4	EAG base case + duration of TE of 5 years	Avapritinib	[redacted]	4.20	[redacted]	2.14	[redacted]
		Midostaurin	[redacted]	2.06			
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	5.50	[redacted]	3.44	[redacted]
		Midostaurin	[redacted]	2.06			
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	6.70	[redacted]	4.64	[redacted]
		Midostaurin	[redacted]	2.06			
7a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log normal) Pessimistic TOT avapritinib (Gompertz) + optimistic TOT midostaurin (exponential) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.70	[redacted]	2.45	[redacted]
		Midostaurin	[redacted]	2.25			
7b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (generalised gamma)	Avapritinib	[redacted]	4.22	[redacted]	2.17	[redacted]

	Large TE jointly (duration of TE of 5 years)	Midostaurin	[redacted]	2.06			
8a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log normal) Pessimistic TOT avapritinib (Gompertz) + optimistic TOT midostaurin (exponential)	Avapritinib	[redacted]	5.32	[redacted]	3.07	[redacted]
	Small TE jointly (duration of TE of 7.5 years)	Midostaurin	[redacted]	2.25			
8b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (generalised gamma)	Avapritinib	[redacted]	4.97	[redacted]	2.91	[redacted]
	Large TE jointly (duration of TE of 7.5 years)	Midostaurin	[redacted]	2.06			
9a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log normal) Pessimistic TOT avapritinib (Gompertz) + optimistic TOT midostaurin (exponential)	Avapritinib	[redacted]	5.72	[redacted]	3.46	[redacted]
	Small TE jointly (duration of TE of 10 years)	Midostaurin	[redacted]	2.25			
9b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (generalised gamma)	Avapritinib	[redacted]	5.56	[redacted]	3.50	[redacted]
	Large TE jointly (duration of TE of 10 years)	Midostaurin	[redacted]	2.06			
10a	Pessimistic OS avapritinib (exponential) + optimistic OS midostaurin (log normal) Pessimistic TOT avapritinib (Gompertz) + optimistic TOT midostaurin (exponential)	Avapritinib	[redacted]	6.18	[redacted]	3.92	[redacted]
	Small TE jointly (duration of TE of lifetime)	Midostaurin	[redacted]	2.25			
10b	Optimistic OS avapritinib (Gompertz) + pessimistic OS midostaurin (exponential) Optimistic TOT avapritinib (Weibull) + pessimistic TOT midostaurin (generalised gamma)	Avapritinib	[redacted]	6.79	[redacted]	4.73	[redacted]
	Large TE jointly (duration of TE of lifetime)	Midostaurin	[redacted]	2.06			
11	EAG base case + PF utility of 0.7	Avapritinib	[redacted]	4.69	[redacted]	2.73	[redacted]
		Midostaurin	[redacted]	3.16			

OS, overall survival; TOT, time on treatment; TE, treatment effect; EAG, external assessment group

Table 8 Cost-effectiveness results of EAG scenario - avapritinib vs 2L+ cladribine

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company updated base case: EAG preferred base case	Avapritinib	[redacted]	3.89	[redacted]	1.86	[redacted]
		Cladribine	[redacted]	2.03			
3a	Pessimistic OS extrapolation for avapritinib: exponential (similar extrapolation to the company's base case) (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.89	[redacted]	1.86	[redacted]
		Cladribine	[redacted]	2.03			
3b	Optimistic OS extrapolation for avapritinib: Log normal (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.50	[redacted]	2.47	[redacted]
		Cladribine	[redacted]	2.03			
3c	Pessimistic OS extrapolation for cladribine: Log logistic (duration of TE of 7.5 years)	Avapritinib	[redacted]	3.90	[redacted]	1.88	[redacted]
		Cladribine	[redacted]	2.02			
3d	Optimistic OS extrapolation for cladribine: Gompertz (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.09	[redacted]	1.94	[redacted]
		Cladribine	[redacted]	2.15			
4	EAG base case + duration of TE of 5 years	Avapritinib	[redacted]	3.85	[redacted]	1.82	[redacted]
		Cladribine	[redacted]	2.03			
5	EAG base case + duration of TE of 10 years	Avapritinib	[redacted]	3.86	[redacted]	1.83	[redacted]
		Cladribine	[redacted]	2.03			
6	EAG base case + duration of TE of lifetime	Avapritinib	[redacted]	3.83	[redacted]	1.80	[redacted]
		Cladribine	[redacted]	2.03			
7a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (Weibull) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.27	[redacted]	2.12	[redacted]
		Cladribine	[redacted]	2.15			
7b	Optimistic OS avapritinib (Log normal) + pessimistic OS cladribine (Log logistic) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 5 years)	Avapritinib	[redacted]	4.12	[redacted]	2.10	[redacted]
		Cladribine	[redacted]	2.02			

8a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (Weibull) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.11	[redacted]	1.96	[redacted]
		Cladribine	[redacted]	2.15			
8b	Optimistic OS avapritinib (Log normal) + pessimistic OS cladribine (Log logistic) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 7.5 years)	Avapritinib	[redacted]	4.51	[redacted]	2.50	[redacted]
		Cladribine	[redacted]	2.02			
9a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (Weibull) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	3.94	[redacted]	1.79	[redacted]
		Cladribine	[redacted]	2.15			
9b	Optimistic OS avapritinib (Log normal) + pessimistic OS cladribine (Log logistic) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of 10 years)	Avapritinib	[redacted]	4.78	[redacted]	2.76	[redacted]
		Cladribine	[redacted]	2.02			
10a	Pessimistic OS avapritinib (exponential) + optimistic OS cladribine (Gompertz) Pessimistic TOT avapritinib (Weibull) + optimistic TOT cladribine (Weibull) Small TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	3.83	[redacted]	1.68	[redacted]
		Cladribine	[redacted]	2.15			
10b	Optimistic OS avapritinib (Log normal) + pessimistic OS cladribine (Log logistic) Optimistic TOT avapritinib (Gompertz) + pessimistic TOT midostaurin (exponential) Large TE jointly (duration of TE of lifetime)	Avapritinib	[redacted]	5.30	[redacted]	3.28	[redacted]
		Midostaurin	[redacted]	2.02			
11	EAG base case + PF utility of 0.6	Avapritinib	[redacted]	3.46	[redacted]	1.65	[redacted]
		Cladribine	[redacted]	1.81			

OS, overall survival; TOT, time on treatment; TE, treatment effect; EAG, external assessment group

5 REFERENCES

1. Blueprint Medicines. *Data on file: ECS IPTW 2023 pooled analysis*; 2024.