

Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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
2. **Company summary of information for patients (SIP)** from Blueprint Medicines
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
 - a. UK Mastocytosis Support Group
 - b. British Association of Dermatologists
 - c. British Society for Haematology
 - d. British Society for Immunology
5. **Expert personal perspectives** from:
 - a. Dr Andrew Whyte – clinical expert, nominated by Blueprint and UK Mastocytosis Support Group
 - b. Dr Deepti Radia – clinical expert, nominated by UK Mastocytosis Support Group
 - c. Jess Hobart – patient expert, nominated by UK Mastocytosis Support Group
 - d. Michelle Shave – patient expert, nominated by UK Mastocytosis Support Group
6. **External Assessment Report** prepared by Kleijnen Systematic Reviews
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Company evidence submission

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Table of abbreviations

Abbreviation	Definition
AdvSM	Advanced systemic mastocytosis
AE	Adverse event
AeDA	German Society of Allergy
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BIC	Bayesian information criterion
BM	Bone marrow
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CEP	Cost-effectiveness plane
CFB	Change from baseline
CI	Confidence intervals
CONSORT	CONsolidated Standards Of Reporting Trial
DALY	Disability-adjusted life-years
DCO	Data cut-off
DoT	Duration of treatment
DSU	Decision Support Unit
ECG	Electrocardiogram
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
ECS	Extended cohort study
EMA	European Medicines Agency
FDA	Food and Drug Administration
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GSTT	Guy's and St Thomas
HCHS	Hospital and community health services
HCP	Healthcare practitioner

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Abbreviation	Definition
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haemopoietic stem cell transplantation
HTA	Health technology assessment
IARC	International Agency for Research and Cancer
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IRP	International recognition procedure
ISM	Indolent systemic mastocytosis
ITT	Intention-to-treat
KOL	Key opinion leader
LDH	Lactate dehydrogenase
LLD	Lower limit
LY	Life-years
LYG	Life-years gained
MaRIH	Maladies Rares Immuno-Hématologique
MC	Mast cells
MCL	Mast cell leukaemia
MCMC	Markov Chain Monte Carlo
MCS	Mental component scores
MDT	Multidisciplinary team
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MW	Molecular weight
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OD	Once daily
OLE	Open-label extension
ONS	Office for National Statistics
OS	Overall survival
OWSA	One-way sensitivity analysis
PAP	Patient assistance programme
PAS	Patient access scheme
PCR	Polymerase chain reaction

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Abbreviation	Definition
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
POM	Prescription-only medicine
PP	Per protocol
PPI	Proton-pump inhibitors
PRISM	Perceptions Realities and Insights on Systemic Mastocytosis
PRO	Patient-reported outcome
PROM	Patient-reported outcome measures
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen ultraviolet
QALY	Quality-adjusted life-years
QD	Quotient-daily
QoL	Quality of life
RCT	Randomised controlled trial
REMA	Spanish Network on Mastocytosis
RU	Resource use
RWE	Real-world evidence
SAE	Serious adverse event
SAF	Symptom assessment form
SC	Subcutaneous
SD	Standard deviation
SDT	Symptom-directed therapy
SE	South-east
SM	Systemic mastocytosis
SmPC	Summary of product characteristics
SSM	Smouldering systemic mastocytosis
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TSS	Total symptom score
TTD	Time to discontinuation
VAF	Variant allele frequency
VAS	Visual analogue scale
VBA	Visual Basic for Application
WHO	World Health Organisation
WTP	Willingness-to-pay

B1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, specifically, adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.¹

Table 1: Decision problem overview

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with inadequately controlled moderate to severe indolent systemic mastocytosis	Adults with inadequately controlled moderate to severe indolent systemic mastocytosis as per marketing authorisation and PIONEER trial population.	Not applicable.
Intervention	Avapritinib as an add-on to standard care	Avapritinib (Ayvakyt®) as an add-on to symptomatic-directed therapy (SDT; also termed best supportive care [BSC] in clinical practice and PIONEER trial).	SDT terminology aligns more accurately with UK and international clinical practice reflecting the lack of specific therapies for patients with ISM.
Comparator(s)	Established clinical management without avapritinib	SDT as the established clinical management without avapritinib. Note should be made that no therapeutic agents are currently approved/reimbursed specifically for ISM in England/ Wales. Current SDT is directed solely at alleviating symptom burden.	SDT terminology aligns more accurately with UK and international clinical practice reflecting the lack of specific therapies for patients with ISM.
Outcomes	The outcome measures to be considered include: • symptom severity • mast cell burden • response rate • adverse effects of treatment • health-related quality of life • mortality	The outcome measures to be considered include: • symptom severity • mast cell burden • response rate • adverse effects of treatment • health-related quality of life • mortality (included as a serious adverse event).	The outcome measures to be included in the company submission are in line with the final scope. Due to the pathogenesis of ISM, mortality is not a key outcome captured in the PIONEER clinical trial, except as part of the safety profile hence the minor amendment.
Economic analysis	• The reference case stipulates that the cost effectiveness of	In line with NICE final scope, however, patient access scheme is	Not applicable.

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	treatments should be expressed in terms of incremental cost per quality-adjusted life-year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.	not confirmed but this is expected to follow a previously agreed discount used in TA1012.	
Subgroups to be considered	No subgroups specified, submission to focus on marketing authorisation.	Blueprint Medicines would like to clarify that this submission covers the full marketing authorisation of avapritinib for the treatment of adult patients with moderate to severe symptoms of ISM inadequately controlled by symptomatic treatment.	Not applicable.
Special considerations including issues	No issues relating to equity or equality raised in the scope.	Blueprint Medicines do not believe that the draft remit or scope will exclude people protected by equality legislation. However, it should be	Not applicable.

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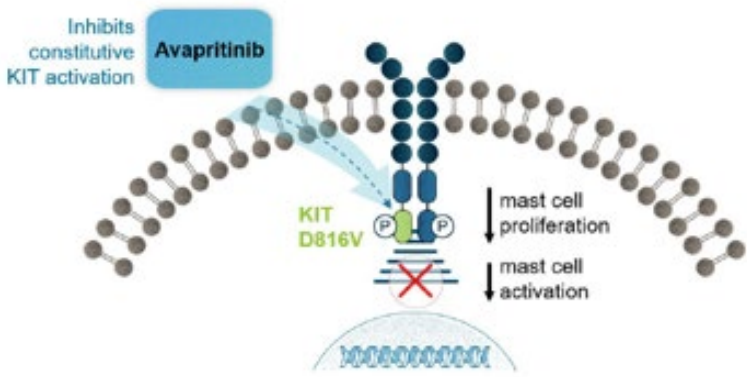
related to equity or equality		noted that, unlike midostaurin, avapritinib does not contain gelatin as an excipient. Inclusion of gelatin can be problematic for people with certain religious or cultural beliefs, particularly those of the Islamic faith for whom this product may not be considered to be Halal. Provision of a gelatin-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.	

Abbreviations: BSC, best supportive care; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SDT, symptom-directed therapy.

1.2 Description of the technology being evaluated

Table 2 presents a brief description of avapritinib for the treatment of moderate to severe ISM inadequately controlled by symptomatic treatments. Appendix A includes the summary of product characteristics (SmPC) full product information on avapritinib as per Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation.

Table 2. Technology being evaluated

UK approved name and brand name	Avapritinib (Ayvakyt®; ATC classification code L01EX18)
Mechanism of action	Avapritinib inhibits the activity of a group of proteins in the body called tyrosine kinases. Specifically, avapritinib is a type 1 tyrosine kinase inhibitor (TKI) that has demonstrated <i>in vitro</i> activity against the <i>KIT D816V</i> variant protein, which is an underlying driver of ISM in ~95% of patients.²⁻⁴ As a type I TKI, avapritinib, potently and selectively inhibits the phosphorylation of <i>KIT D816V</i>, with a half maximal inhibitory concentration (IC₅₀) of 0.27 nM.⁵ Other type I TKIs such as dasatinib and midostaurin are considered less potent than avapritinib against <i>KIT D816V</i> mutations with higher IC₅₀ concentrations (1.6 nM and 2.7 nM respectively) indicating weaker inhibition.⁵ 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.^{1,5} 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 <i>KIT D816V</i> variant protein-mediated receptor dimerisation (Figure 1).⁶ Figure 1. Mechanism of action of avapritinib  The diagram illustrates the mechanism of action of avapritinib. It shows a KIT D816V receptor dimerizing and activating downstream pathways leading to mast cell proliferation and activation. Avapritinib is shown inhibiting this constitutive activation. Source: Adapted from Gilreath et al. 2019⁷; Evans et al. 2017⁵; Bauer et al. 2021⁶

Marketing authorisation/CE mark status	In May 2023, avapritinib was initially approved by the FDA for the treatment of adult patients with ISM.⁸ Avapritinib received EU marketing authorisation in December 2023 as the first and still the only treatment for adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.⁹ An application for marketing authorisation through the international recognition procedure (IRP) route was submitted to the MHRA on [REDACTED] X. Anticipated date of GB marketing authorisation is [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Avapritinib is anticipated to be indicated for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment (see SmPC in Appendix A).¹ As per the SmPC, avapritinib is currently indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.¹ Additionally, avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).¹
Method of administration and dosage	For ISM, the recommended dose of avapritinib is 25 mg orally once daily on an empty stomach. This is the maximum recommended dose that must not be exceeded in patients with ISM. Treatment of ISM should be continued until disease progression or unacceptable toxicity occurs. Concomitant use of avapritinib with strong or moderate CYP3A inhibitors must be avoided.¹
Additional tests or investigations	No additional tests are required for identification of eligible patients. Before administration of avapritinib, healthcare providers should consider the risk for worsening cognitive effects, localised (peripheral, facial) oedemas (common frequency) and QT interval prolongation in patients with ISM.¹
List price and average cost of a course of treatment	The list price of avapritinib (25 mg) as a prescription-only medicine (POM) is £26,667.00 (as per BNF).¹⁰ The average cost for a course of treatment at PAS price is estimated to be [REDACTED]
Patient access scheme (if applicable)	Currently, there is a simple discount PAS for avapritinib (as per AdvSM NICE submission).¹¹ This PAS discount price for avapritinib has been included in the economic analyses in this submission.

Abbreviations: AdvSM, advanced systemic mastocytosis; ATP, adenosine triphosphate; BM, bone marrow; BNF, British National Formulary; EMA, European Medicines Agency; FDA, Food and Drug Administration; IC50, half maximal inhibitory concentration; IgG, immunoglobulin G; IRP, international recognition procedure; ISM, indolent systemic mastocytosis; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, patient access scheme; SmPC, summary of product characteristics; TKI, tyrosine kinase inhibitor; US, United States

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

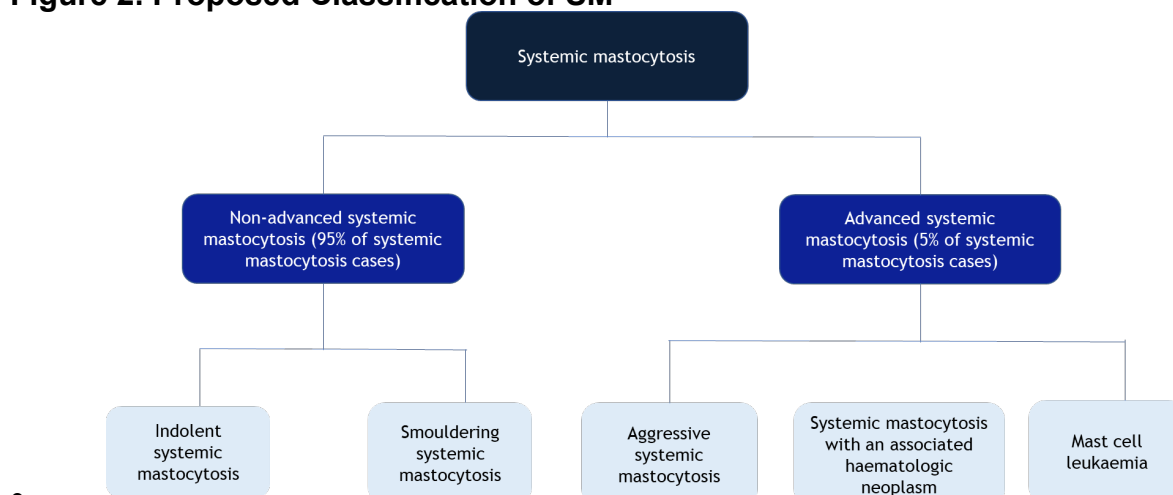
1.3.1 ISM overview

Systemic mastocytosis (SM) is a rare haematologic neoplasm associated with unchecked proliferation and activation of mast cells (MCs) with organ infiltration into the bone marrow, liver, spleen, lymph nodes and the gastrointestinal (GI) tract.¹² Indolent systemic mastocytosis (ISM), a subtype of non-advanced SM represents 95% of adults with SM, with the remainder classified as advanced SM (AdvSM).^{3,13} ISM, a rare clonal MC disease, is driven in ~95% of cases by *KIT D816V* mutation which drives the accumulation and hyperactivity of mast cells, leading to excessive signalling of vasoactive and inflammatory cytokines, including leukotrienes, prostaglandins, and interleukins.¹⁴ Broad, heterogeneous symptoms (skin, GI, anaphylaxis and osteoporosis) contribute to considerable disease burden including poor clinical outcomes and reduced health-related quality of life (HRQoL).¹⁵⁻¹⁷ In conjunction with comorbidities associated with ISM, symptoms further exacerbate limitations in daily activities (such as productivity) and elevate mortality risk compared to the general population.^{15,18-21}

1.3.2 Disease definition and classification of SM

In terms of SM, commonly used groupings include the following subtypes (Figure 2): non-advanced SM (95% of SM cases) including ISM and smouldering SM (SSM); and advanced SM (AdvSM; 5% of SM cases).²² Subtypes of AdvSM are comprised of aggressive SM (ASM), SM with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL).²²

Figure 2. Proposed Classification of SM



Abbreviations: SM, systemic mastocytosis.

Sources: Pardanani et al. (2021)²³; Pardanani et al. (2023)²²; Valent et al. (2017).²⁴

1.3.3 WHO diagnostic criteria for SM

For the diagnosis of SM, criteria have been established by the World Health Organisation (WHO) to identify aberrant MCs in various tissues (Table 3).^{22,25} This classification of SM (and subsequently ISM) is stipulated in diagnostic guidelines and was used in the pivotal PIONEER (NCT03731260) clinical trial for eligibility purposes.^{22,25,26} These criteria are based on defined pathological and laboratory criteria including 4 minor criteria (atypical MCs, KIT mutation, CD2/CD25 expression on MCs or elevated serum tryptase) and 1 major criterion (dense MC infiltrates). An SM diagnosis is established if at least 1 major and 1 minor criteria or 3 minor criteria are satisfied.^{22,27}

Table 3. WHO diagnostic minor criteria for SM

Major criterion
• Multifocal dense infiltrates of MCs (≥ 15 MC aggregates) in bone marrow or other extracutaneous organs
Minor criteria
• In biopsy sections of bone marrow or other extracutaneous organs, $>25\%$ of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all MCs in bone marrow aspirate smears, $>25\%$ are immature or atypical
• Detection of KIT-activating KIT point mutation at codon 816 of <i>KIT</i> in bone marrow, blood or other extracutaneous organs
• MCs in bone marrow, blood or other extracutaneous organ express CD25 with/without CD2 in addition to normal MC markers
• Baseline serum total tryptase concentration ≥ 20 ng/mL

Note: WHO diagnostic criteria (2017) used as eligibility criteria for PIONEER pivotal clinical trial.^{26,27}

Abbreviations: MC, mast cells; SM, systemic mastocytosis; WHO, World Health Organisation.

Source: Valent et al. (2023)²⁵; Pardanani et al. (2023).²²

In addition to these criteria, SM is further differentiated based on degree of disease burden (B-findings) and organ damage (C-findings) in addition to adverse pathological issues.^{22,25,28} Table 4 summarises the B-findings and C-findings which are essential for differentiation of ISM from more advanced forms of SM.^{22,25} Noteworthy updates from WHO (2017)²⁷ criteria included broadening of B-finding criteria as well as patients with *KIT* D816V variant allele frequency (VAF) $\geq 10\%$ in bone marrow (BM) or peripheral blood (PM) leukocytes in recent diagnostic guidelines.^{22,23,28}

Table 4. WHO B-findings and C-findings criteria of SM

B-Findings	C-Findings
- High MC burden: MC infiltration in BM >30% by histology <i>and/or</i> serum tryptase >200 ng/mL <i>and/or</i> <i>KIT D816V VAF ≥10% in BM or PB leukocytes.</i> - Signs of myeloproliferation and/or myelodysplasia: Hypercellular BM with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPN. - Organomegaly: hepatomegaly, splenomegaly, or palpable lymphadenopathy (on CT or ultrasound: >2 cm) without impaired organ function.	- Cytopenia: Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by ≥1 cytopenia(s) (ANC <1.0 × 10⁹/L, Hgb <10 g/dl, and/or platelet count <100 × 10⁹/L). - Hepatopathy: Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension. - Bone: Skeletal involvement with large (≥2 cm) osteolytic lesions with/without pathological fractures caused by osteoporosis do not qualify as a “C” finding. - Spleen: Palpable splenomegaly with hypersplenism. - GI tract: Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

Note: WHO diagnostic criteria (2017) used as eligibility criteria for PIONEER pivotal clinical trial.^{26,27} Updates from WHO (2017) criteria to WHO (2022) criteria denoted by italicised wording in B-findings column.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CT, computed tomography; MC, mast cell; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; VAF, variant allele frequency; WHO, World Health Organisation.

Source: Valent et al. (2023, 2024)^{25,28}; Pardanani et al. (2023)²²

1.3.4 Diagnostic pathway for ISM

Diagnostic classification according to the WHO criteria differentiates ISM from advanced forms of SM (ASM, SM-AHN, and MCL) by the absence of end-organ damage, abnormal haematological and biochemical parameters (C-findings), and significant organomegaly (Table 4).^{22,25,28,29} Due to the wide variability in non-specific symptoms among patients, diagnosing ISM is frequently delayed.^{18,30} The involvement of multiple organ systems often leads patients to consult a range of healthcare specialists, contributing to underdiagnosis and a diagnostic delay that can span 5 to 9 years from the initial onset of symptoms.^{18,30} Further, according to findings from the Perceptions Realities and Insights on Systemic Mastocytosis (PRISM) study (n=540), 28% of people living with ISM experienced a delay of at least 5 years before receiving a confirmed diagnosis.³⁰

Patients with ISM are typically reported to have low mast cell infiltration in bone marrow, *KIT D816V* mutation (as assayed by polymerase chain reaction [PCR] testing) and a serum tryptase concentration ≥20 ng/mL. As per the established WHO criteria (Table 3), patients exhibiting <2 B-findings and no C-findings are diagnosed

with ISM.^{22,25,28} This aligns with the pivotal PIONEER clinical trial which recruited patients using this algorithm for eligibility screening.³¹

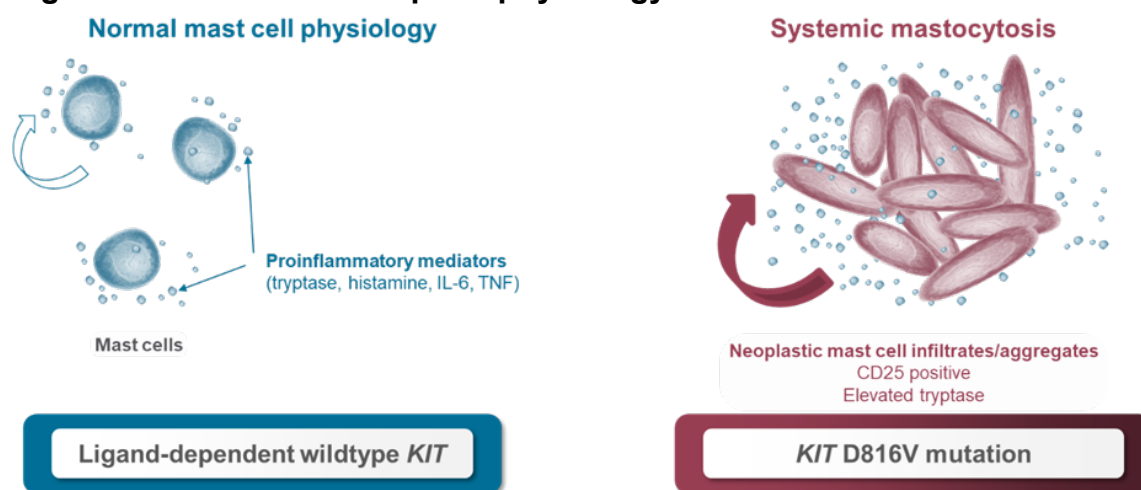
Clinical guidelines specified by the European Competence Network on Mastocytosis (ECNM) include recommendations for monitoring serum tryptase concentrations and *KIT* D816V mutations when SM is suspected.³² Diagnostic testing should be considered alongside other clinical and laboratory findings (as per WHO diagnostic criteria; see Table 3 and Table 4) for clinical accuracy.³²

1.3.5 Aetiology and pathophysiology of ISM: driving factors

1.3.5.1 *KIT* D816V mutation

Mast cell differentiation, proliferation, maturation, and functioning is dependent on ligand-dependent *KIT* signalling throughout their development.³³ Activation of *KIT* signalling triggers the release of proinflammatory, degranulation mediators (including tryptase, histamine, IL-6 and tumour necrosis factor [TNF]).^{33,34} The underlying pathophysiology of ISM is likely attributed to an activating mutation of *KIT* (*KIT* D816V) in MCs (Figure 3).²⁻⁴

Figure 3. Overview of ISM pathophysiology



Source: Adapted from Theoharides et al (2015)¹²; Pardanani et al (2021)²³; and Garcia-Montero et al (2006)²

In 95% of ISM cases, the *KIT* D816V mutation has been identified in peripheral blood or BM at diagnosis resulting in the accumulation of mast cell aggregates in BM or/and other extracutaneous organ(s).^{12,22,23} Constitutive activation of *KIT* D816V

gene mutation triggers greater disease activity, uncontrolled proliferation and mast cell activation.²⁻⁴

1.3.5.2 Serum tryptase

As a mast cell mediator, elevated baseline serum tryptase level is a long-established key characteristic of ISM with a progressive concentration increase associated with elevated symptom severity and a worsening prognosis.³⁵⁻³⁷ As per WHO classification guidelines, serum tryptase levels >20 ng/mL is a minor diagnostic criterion for ISM.^{22,28} Disease worsening from mild symptom burden to moderate-severe symptom burden as well as progression to more advanced disease forms (such as SSM or AdvSM) is elevated in patients with ISM who have *KIT D816V* mutation, increased serum tryptase levels and high symptom burden.^{3,37,38}

1.3.6 Epidemiology

1.3.6.1 Prevalence and incidence

Avapritinib was granted orphan designation by the European Medicines Agency (EMA) for the treatment of mastocytosis.³⁹ Individual country prevalence from a Danish study aligns with this orphan designation with 18 cases of ISM per 100,000 people equating to 80% of total SM cases.⁴⁰ Orphanet, a portal for rare diseases, provided an estimation of ISM prevalence ranging between 9.6 and 13.0 cases per 100,000 persons in Europe.⁴¹ This estimation is corroborated by another recent Danish nationwide register study (data up to January 2022) which reported the prevalence of ISM at 9.36 per 100,000 persons (95% CI: 8.51–10.28), and average incidence rate at 0.43 per 100,000 persons per year (95% CI: 0.32-0.55).⁴²

While detailed data on the prevalence and incidence of ISM in UK is not available, clinical experts as part of the UK Mastocytosis Support Group (patient advocacy group [PAG]) estimate 1 in 10,000 people may suffer from ISM.⁴³ This aligns with individual European country estimation of ISM patient populations and is consistent with NHS clinical expectations.⁴⁴

Furthermore, in lieu of specific UK epidemiological data, other country sources can be used for estimation of the proportions of moderate to severe patients with ISM. For instance, the CEREMAST study conducted in France reported 5,834 patients with mastocytosis of which 2,975 had ISM (51%).⁴⁵ From this survey, the French ISM

population (defined as ISM and mastocytosis in skin [MIS]) was estimated to be 4,259 patients with 2,257 (53%) experiencing moderate to severe symptoms.⁴⁵ Of these patients, 813 (36%) were not adequately controlled with symptomatic treatment representing a distinct therapeutic unmet need.⁴⁵

1.3.6.2 Mortality

Symptom burden and comorbidities in patients with ISM contribute to an elevated risk of mortality. Compared to AdvSM, ISM was long thought to have little impact on mortality. However, emerging data on large numbers of patients with ISM (US claims dataset) indicates excess mortality compared to general population (matched non-SM control cohort; overall survival [OS] hazard ratio [HR] of 1.64).²¹ Similarly, a Danish population-based cohort study compared the 5-year survival of patients with SM (n=1,275) to that of the general population of Denmark (age- and sex-matched controls, n=14,610).²⁰ Focusing specifically on the subset of patients with ISM and comparing to the control group, the age- and sex-adjusted risk of death was significantly higher in the group with ISM, with a reported hazard ratio of 2.59 (95% CI: 2.14, 3.14).²⁰ As per clinical expert feedback, this Danish cohort of patients with ISM and its reduced life expectancy is reflective of UK patient population.⁴⁴

A recent retrospective cohort analysis from the US compared OS of a large sample of 8,332 patients with ISM with 3 control groups (n=6,000) matched by sex, age, Charlson Comorbidity Index, payer status and race/ethnicity.²¹ The study showed that patients with ISM had statistically significantly worse OS compared with the matched controls (HR: 1.70; 95% CI: 1.39, 2.10; p<0.0001). This study shows that acute, severe symptoms of SM may contribute to the excess mortality seen among patients with ISM.²¹

Furthermore, UK clinicians (as per structured expert elicitation) acknowledge that individuals with ISM face an elevated mortality compared to the general population, emphasising that symptoms do not necessarily correlate with tryptase levels or predict mortality risk.⁴⁴ Notably, clinicians highlighted no significant mortality difference between mild, moderate, and severe ISM patients signifying a lack of correlation with symptom severity.⁴⁴

1.3.7 Clinical presentation and burden of disease

ISM is characterised by MC infiltration in skin and at extracutaneous sites such as bone marrow, liver, spleen, lymph nodes and GI.⁴⁰ Clinical manifestations at different sites are caused by growth and infiltration of the MCs in various organs as well as mediator release by aberrant MCs, including inflammatory mediators including histamines, leukotrienes, prostaglandins, heparin and interleukins (IL-6).^{18,22}

Mediators are released in response to a variety of triggers such as exposure to food, infection, natural and chemical odours, physical stimuli (heat, cold, friction, sunlight, etc.), physical exertion, bacterial proteins, venom, medication (non-steroidal anti-inflammatory drugs, general anaesthetics) and stress.⁴⁶

This results in the broad, heterogeneous symptom profile observed in people living with ISM which may include diarrhoea, pruritus, abdominal pain, nausea, headache flushing, cognitive impairment, fatigue, bone pain, and skin lesions.^{12,15,18,30,47} In turn, these persistent, debilitating symptoms predominate their day-to-day living with negative impacts on emotional wellbeing, HRQoL and their ability to function normally.^{18,19,30,48}

1.3.7.1 Symptom burden in ISM

With the unpredictable nature of mediator release from aberrant MCs, the burden presented by heterogeneous ISM symptomatology is considerable. There is substantial variation in symptom severity (mild, moderate or severe) and type (skin, GI, osteoporosis and anaphylaxis) reported in patients. The majority of patients (60-70%) with ISM experience moderate to severe symptoms as per PRISM study.^{15,49} Of these patients with moderate to severe symptoms, there is a distinct subset (~36%) that are not adequately controlled with symptomatic treatments representing a distinct area of unmet need.⁴⁵

1.3.7.1.1 ISM symptom profile

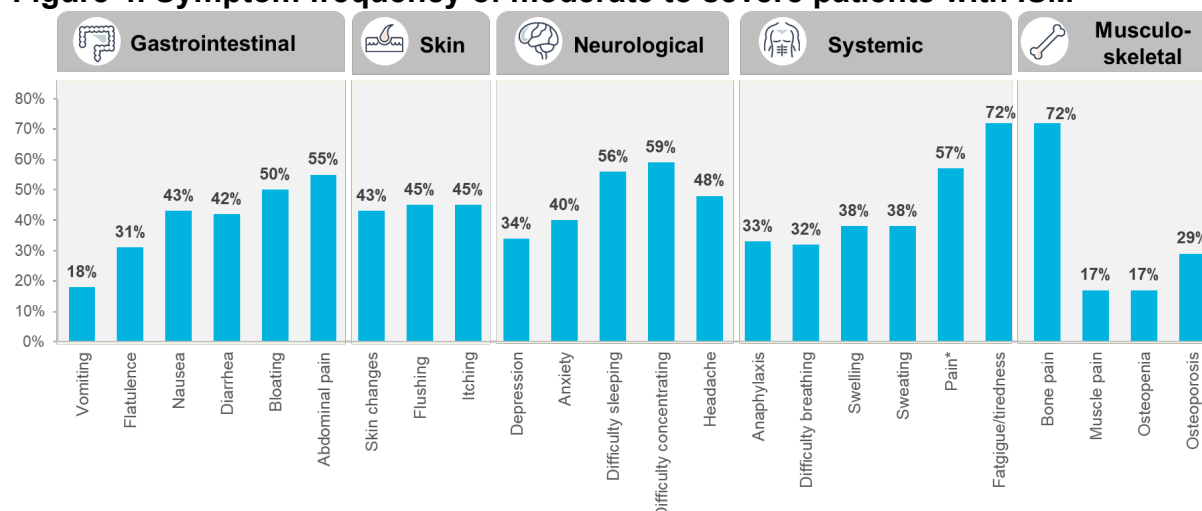
The heterogenous nature of ISM is demonstrated by a wide range of symptoms varying in frequency and intensity. A patient-reported registry, Mast Cell Connect Registry) supports this rationale with data from 88 patients with moderate to severe symptoms within the past year (Figure 4).¹⁸ Symptoms of ISM were associated with

systemic, skin, GI, respiratory, musculoskeletal and neuropsychiatric systems with the most common including fatigue (72%) and abdominal pain (55%).¹⁸

Similar findings from the European PRISM study reported the most bothersome symptoms experienced by patients with ISM were skin-related ([17%] hives, itching, spots on skin and flushing), gastrointestinal-related ([20%] stomach bloating, nausea/vomiting, heart burn, gastroesophageal reflux, change in bowel movements, abdominal/stomach pain and stomach cramps) and anaphylaxis.³⁰

Problematic episodes of anaphylaxis are caused by extensive release of mediators by aberrant MCs.⁵⁰ These events are potentially life-threatening with the PRISM study reporting 44.7% of people with ISM experienced an anaphylactic reaction that required treatment or immediate medical attention.¹⁵

Figure 4. Symptom frequency of moderate to severe patients with ISM



Abbreviations: ISM, indolent systemic mastocytosis.

Source: Adapted from Mast Cell Connect Registry survey results as published by Jennings et al. (2018).¹⁸

1.3.7.1.2 ISM-SAF severity classification

As it stands there is no standardised system for the evaluation of symptom severity scoring or definition of disease management with variation in patient-reported outcome measures (PROMs) available.⁵¹ Given the uniqueness/varying symptomology of ISM that cannot be captured through other generic questionnaires, ISM Symptom Assessment Form (ISM-SAF®; Blueprint Medicines Corporation) was designed specifically with input from disease experts, patients, and regulatory

authorities as a clinical treatment outcome measure to support regulatory approval and reimbursement.⁵¹⁻⁵³

ISM-SAF is a psychometrically validated, clinically relevant PRO tool used to measure symptom burden including the severity.⁵¹⁻⁵³ With its 12-item daily diary (including 11 symptom severity items and diarrhoea frequency as the 12th item), ISM-SAF is used to report the severity of 11 ISM symptoms (Table 5) over a 24 hour recall period, yielding a total symptom score (TSS) ranging from 0 to 110. Scoring at item, domain and total score level provides insights into patient symptom burden with a ≥28-point threshold indicating moderate to severe symptoms. Higher scores are reported in cases of greater symptom severity.^{49,51,54}

Table 5. ISM-SAF domains and scales

ISM Symptom Assessment Form (ISM-SAF)		
Domain	Symptom	Scoring
GI domain (0-30)	Abdominal pain Diarrhoea (severity) Nausea	Patients are analysed as a 14-day moving average or one-time (dependent on clinic) Each symptom is scored 0–10 with: ○ 0 = no [symptom] ○ 10 = worst imaginable [symptom] Individual symptom severity scores are summed to generate a TSS (0–110) Additional question asked regarding diarrhoea frequency (12 th item)
Skin domain (0-30)	Spots Itching Flushing	
Neurocognitive symptoms (0-30)	Brain fog Headache Dizziness	
	Bone pain Fatigue	

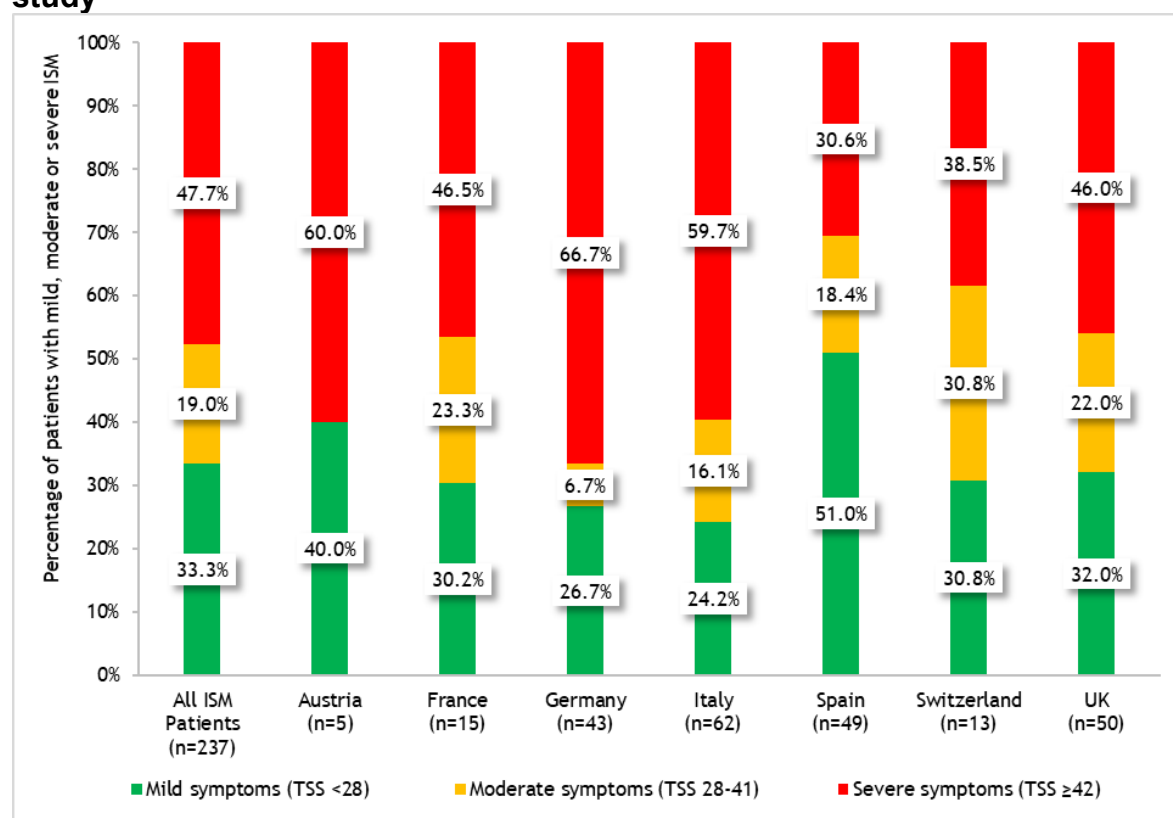
Abbreviations: ISM, indolent systemic mastocytosis; SAF, standard assessment form; TSS, total symptom score.
 Source: Adapted from PIONEER Clinical Study Summary and PRISM survey.^{49,54}

The ISM-SAF assessment tool has been validated through 3 different cohorts of patients with ISM (including the PIONEER study) demonstrating reliability, accuracy and correlation with other outcome assessments assessing impaired physical function, emotional wellbeing and quality of life.^{52,53,55} To evaluate the efficacy of avapritinib in the ongoing PIONEER clinical trial (NCT03731260), mean change in ISM-SAF TSS from baseline to 24 weeks on treatment serves as the primary endpoint.²⁶ Notably, the PIONEER trial was used to confirm the utility of the PRO measure of ISM symptomology with baseline TSS symptom scores indicating high

symptom burden despite optimised SDT in both avapritinib (score of 50.2) and placebo (score of 52.4) groups.^{31,54}

Data from the European PRISM survey study (n=237) showed that 67% of all included patients with ISM reported moderate to severe symptoms (TSS $\geq$ 28) and 48% reported severe symptoms (TSS $\geq$ 42) (Figure 5).¹⁵ Across all 7 countries (Austria, France, Germany, Italy, Spain, Switzerland and UK) included in the PRISM study, the mean TSS of the patients with ISM was 40.5. According to PRISM survey results, people in the UK living with ISM (n=50) had predominantly moderate to severe symptoms (68%).¹⁵

Figure 5. ISM-SAF TSS severity amongst patients with ISM in European PRISM study



Note: The Perceptions Realities and Insights on Systemic Mastocytosis (PRISM) study was a survey conducted in patients with SM and healthcare providers in 7 European countries (Austria, France, Germany, Italy, Spain, Switzerland and the UK). The aim of the study was to assess symptom burden and HRQoL associated with non-advanced and advanced SM. The patient survey consisted of 119 questions and a total of 540 patients with SM participated; of these, 237 had ISM. The physician survey included 103 questions and was completed by a total of 618 participants. Abbreviations: ISM, indolent systemic mastocytosis; TSS, total symptom score. Source: Data on file. Blueprint Medicines Corporation. PRISM (2023).¹⁵

1.3.7.1.3 ISM-SAF in NHS clinical practice

While currently not licensed for routine use in clinical practice, the ISM-SAF tool has been validated in patients with ISM managed by the UK Mastocytosis Centre of Excellence Guy's and St Thomas' (GSTT) hospital.⁵⁶ Of 76 patients assessed with ISM-SAF over a 4-week period, 33 patients (43%) attained a TSS $\geq$ 28 corresponding to the threshold for moderate to severe symptoms (as per psychometric analysis and PIONEER clinical trial).^{31,53,56} Notably, the highest scoring symptoms were fatigue and skin spots with mean scores of 4.66 and 3.97 respectively. The ISM-SAF symptom burden observed in this cohort is consistent with that of NHS-treated ISM patients in routine clinical practice.⁵⁶

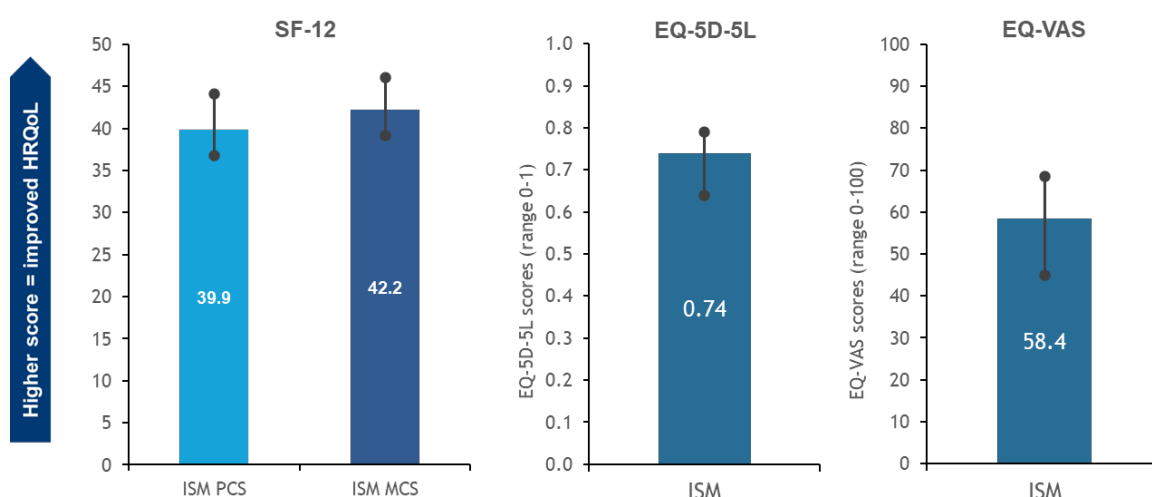
Corroborating these findings, clinical experts acknowledge that ISM-SAF severity definitions are broadly aligned with clinical practice, though real-world assessment is based on global judgement of HRQoL, impact of daily activities, and most burdensome symptoms.⁴⁴

1.3.7.2 ISM symptom burden impact on HRQoL

The constellation of symptoms exhibited by people living with ISM, particularly moderate to severe, leads to a significant reduction in HRQoL according to studies in Europe and US.^{19,57} The majority of patients reported that they had to reduce their work hours,^{18,19} impairment in performing activities of daily living,^{18,48} and that the symptoms of ISM interfered with their social relationships.⁴⁸

In the PRISM study (N=540), HRQoL was assessed via the 12-Item Short Form Health Survey (SF-12) physical (PCS) and mental component scores (MCS), the EuroQoL-5 dimension-5 level (EQ-5D-5L) questionnaire and the EuroQoL visual analogue scale (EQ-VAS) (Figure 6). Of this study cohort, 237 patients with ISM (44%) responded to the PRISM survey. SF-12 components showed substantially impaired HRQoL in people living with ISM, with mean PCS scores of 39.9 and MCS scores of 42.2, both well below the average for healthy individuals (50.1). EQ-5D-5L scores for ISM patients were 0.7 and EQ-VAS scores were 58.4, compared to population norms for France, Germany, Italy, Spain and the UK for patients aged 45-54 years (EQ-5D-5L ~0.9; EQ-VAS ~80).⁴⁹

Figure 6. PRISM study reported HRQoL in people living with ISM



Note: 237 ISM patients (44% of 540 total respondents) were included in the PRISM cohort. Vertical line denotes the range of mean scores reported from France, Germany, Italy, Spain and the UK. Abbreviations: EQ-5D-5L, 5-level EuroQoL Five-Dimension; EQ-VAS, EuroQoL Visual Analogue Scale; ISM, indolent systemic mastocytosis; MCS, mental component score; PCS, physical component score; SF-12, 12-Item Short Form Health Survey. Source: Adapted from Triggiani et al. (2025)³⁰.

1.3.7.2.1 Disability-adjusted life-years as a measure of disease burden

As previously stated, the high symptom burden in ISM (particularly in moderate to severe patients) impacts daily activities and HRQoL with profound effects on psychological, emotional and overall wellbeing (refer to Section 1.3.7.2).

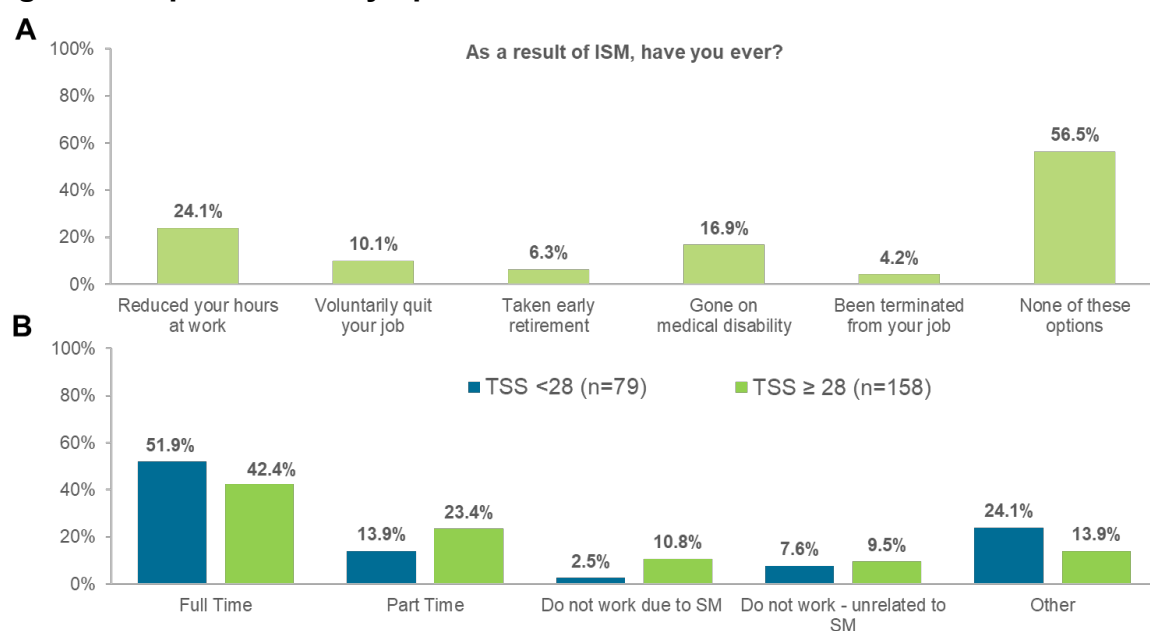
Indeed, this significant burden has been recently quantified in a prospective/retrospective study at CEREMAST (French expert centre) with the calculation of disability-adjusted life-years (DALYs).⁵⁸ In this study, DALYs were used to assess overall disease burden as cumulative number of years lost due to ill-health, disability of early death. On average 12.7 (± 5.9) symptoms per patients were reported with marked effects on quality of life (QoL), emotional and social wellbeing. DALYs ranged between 4.56 to 8.79 (89 to 168 per 100,000 inhabitants) which is comparable to lymphoma, leukaemia and psoriasis. These findings highlight the need to improve management to improve the considerable symptom burden and impact on patients' QoL.⁵⁸

1.3.7.3 ISM symptom burden impact on ability to work

In the PRISM study, people living with ISM reported a significant impact on their ability to work (Figure 7). For UK patients (n=50), 50% of patients reported that ISM had a meaningful impact on their ability to work, with 32% reducing hours, 16%

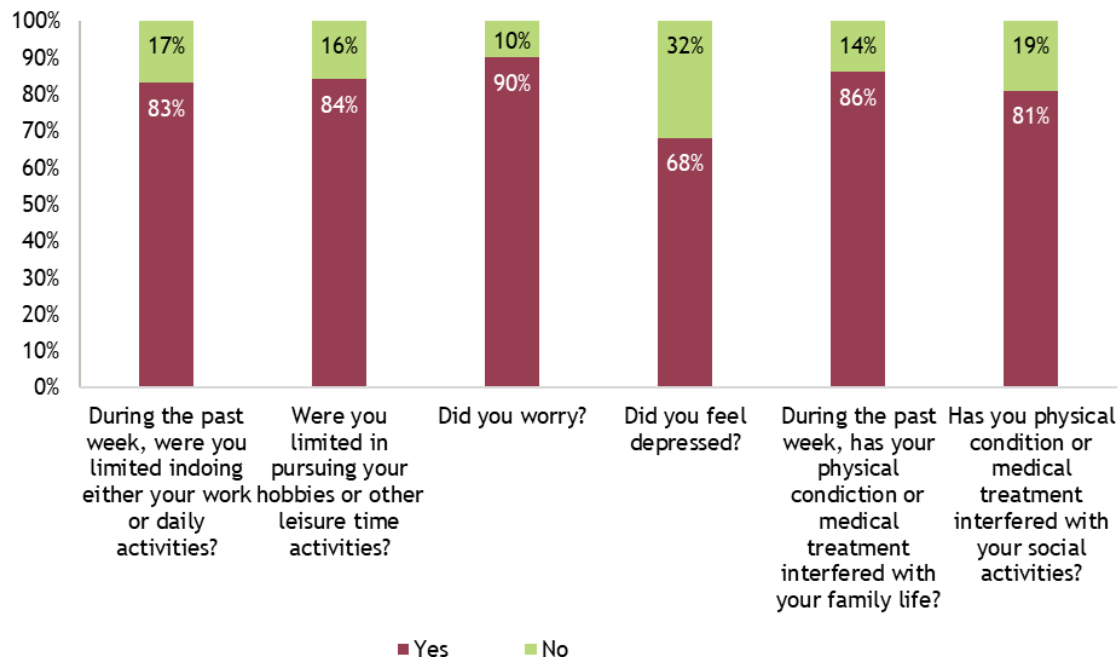
voluntarily quitting and 18% going on medical disability.⁴⁹ As part of the PRISM, people living with ISM (and their physicians) highlighted how the disease and related symptom burden impacted activities of daily living (according to a score scale of 1 [strongly disagree] to 7 [strongly agree]). Of note, many people with ISM reported avoidance of leaving the house (mean score 4.7) and isolation due to their symptoms (mean score 4.5). Overall, patients rated the impact on daily living with a mean score of 3, equivalent to activities of daily living somewhat affected by the disease.¹⁵ These findings are corroborated by similar trends observed in the cross-sectional TouchStone US survey with almost 64% reporting avoidance of leaving the house due to SM.¹⁹ Additionally, according to the Mast Cell Connect patient registry, over 80% of patients with ISM (n=88) considered themselves limited in their ability to work or perform daily activities due to symptom burden (Figure 8).¹⁸

Figure 7. Impact of ISM symptom burden on work status



Note: A. Presents patient responses to a PRISM survey question; B. Differentiation of patient working pattern in ISM patients with TSS <28 and TSS ≥28. Abbreviations: ISM, indolent systemic mastocytosis; PRISM, Perceptions Realities and Insights on Systemic Mastocytosis; SM, systemic mastocytosis; TSS, total symptom score. Source: Adapted from Blueprint Medicines Corporation PRISM [Data on file] and EAACI PRISM (2024).⁴⁹

Figure 8. Impact of symptoms on daily life of people with ISM



Abbreviations: ISM, indolent systemic mastocytosis.

Source: Adapted from Mast Cell Connect Registry survey as published by Jennings et al. (2018).¹⁸

1.3.7.4 Comorbidities

From a small number of studies reporting comorbidities, people living with ISM suffer from a high baseline burden of comorbidities which adds to the considerable symptom burden negatively impacting daily living and HRQoL.^{15,19,58,59}

Overall, the evidence available on the burden of comorbidities in people with ISM in the UK is limited. As part of the aforementioned European PRISM survey, people with ISM (n=237), reported comorbidities including skin lesions of mastocytosis (14%), mast cell activation syndrome (2%), Ehlers-Danlos syndrome (2%), postural orthostatic tachycardia syndrome (2%), and hereditary alpha tryptasemia (0.8%).³⁰ Similarly, data from a recent PRO survey (TouchStone™) revealed SM patients (N=56; 66% with ISM) reported notably high proportions of comorbidities including POTS (34%), EDS (30%), osteopenia/osteoporosis (29%), diabetes (11%) and HaT (7%) diagnoses.¹⁹

Real-world evidence (RWE) from US claims data (n=333) highlighted typical baseline comorbidities including hypertension (58%), malignancy (43%) and COPD (36%) in patients with non-AdvSM (including ISM).⁵⁹ Another US retrospective US study using

PharMetrics® Plus database (n=170 non-AdvSM), the most common baseline comorbidities included cancer (28%), anxiety (26%), asthma (16%) and depression (15%).⁶⁰ Consequently due to this comorbidity burden, patients with moderate to severe ISM reported significantly higher healthcare resource use (HCRU) compared to non-SM controls. As a result, patients with moderate to severe ISM were found to have more than double the mean number (SD) of emergency department visits (3.11 [SD 11.18] vs. 1.23 [SD 2.65]; p=0.001), a higher hospitalisation rate (43.0% vs. 27.6%; p<0.0001), longer hospital stays (6.16 [SD 16.07] vs. 3.47 [SD 12.89] days; p=0.0016), and increased epinephrine injector prescriptions (5.3 [SD 6.8] vs. 2.9 [SD 1.8] per person), compared to controls.⁶⁰

1.3.7.5 Progression of ISM

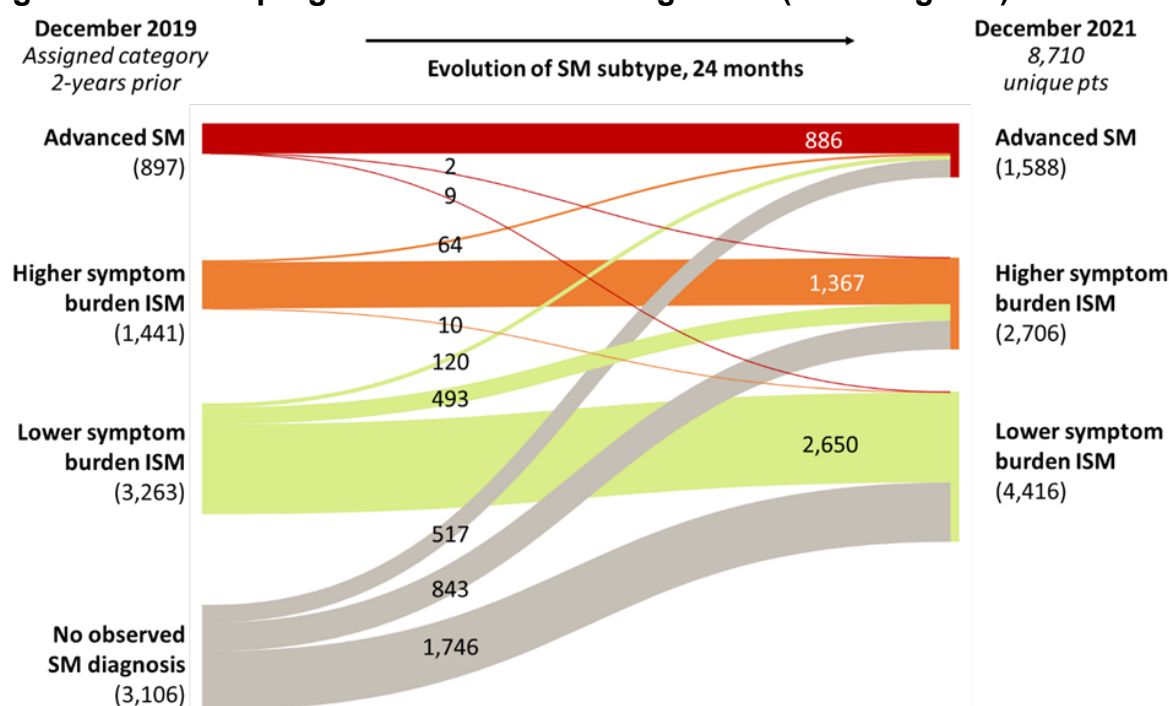
Risk factors for progression from ISM to more advanced disease (SSM and AdvSM) include increased serum tryptase levels, inflammatory mediators, the presence of high levels *KIT D816V* VAF, and high symptom burden (as per ISM-SAF TSS).^{3,37,61} According to a large-scale ECNM patient cohort study, multivariate analysis showed a higher risk of progression to more advanced disease and death significantly associated with male patients, worse performance status (activity level) and organomegaly.¹⁷ These findings underscore the clinical relevance of disease progression with understanding that the proportion of patients progressing to AdvSM is small (2.9%).¹⁷

A large study by Mukherjee et al. (2023) based on US claims data (2019-2022) tracked patients with higher symptom burden (n=2,706) as they progressed to advanced ISM (4.4%). Data showed that a considerable proportion of ISM patients (15%) with mild symptoms experienced disease worsening to severe ISM within a timeframe of 2 years.³⁸ With no disease-modifying therapies approved by NICE, patients inadequately controlled with SDT symptomatic therapies will likely progress to more advanced forms of mastocytosis.³⁸

UK clinical experts have highlighted that ISM does not follow a predictable linear pathway where patients systematically move from mild to moderate to severe ISM and then to more advanced forms of mastocytosis, as the majority of patients with symptomatically mild ISM will fluctuate between mild, moderate and severe. The

experts also reported that patients cannot spontaneously improve from severe to moderate symptoms without medical intervention, meaning that any backwards movement in disease severity only occurs as a result of effective treatment rather than natural disease course.⁴⁴

Figure 9. Disease progression and worsening of SM (including ISM)



Abbreviations: ISM, indolent systemic mastocytosis.

Source: Mukherjee et al. (2023).³⁸

1.3.8 ISM clinical pathway of care

1.3.8.1 Treatment guidelines

Clinical guidance for SM (including ISM) is based on an individualised treatment approach for ISM due to its heterogeneity and the burden of symptoms stemming from involvement of skin (e.g. pruritus, flushing), gastrointestinal (GI) tract (e.g. diarrhoea, constipation) as well as osteoporosis and/or anaphylaxis.^{45,62,63} ECNM-AIM international guidelines (published in 2022) provides recommendations for first-line therapy for these symptom areas aligning with country-specific guidelines.^{29,64}

There are currently no UK-specific guidelines for the management of patients with ISM. Current information provided by NHS England⁶⁵ are for SM in general (non-specific for ISM) which is a trend observed for other European countries including Germany, Spain and the Nordics.^{62,63,66} ISM-specific guideline recommendations are

Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

provided by a 2022 French guideline which details the use of cytoreductive agents (interferon and cladribine) and off-label use of omalizumab (anti-IgE agent) in the event of inadequate symptom control.⁴⁵

The German Society of Allergy (AeDA) published a comprehensive position paper in 2025 specifically addressing the management of ISM in the era of precision medicine.⁶⁷ The AeDA recommendations place emphasis on that ISM management requires a coordinated, interdisciplinary strategy focusing on symptom control and enhancement of patient QoL. This outlines a structured symptomatic treatment approach for ISM, centred on second-generation H1 antihistamines (up to 4 times the standard dose if needed), with H2 blockers for gastrointestinal symptoms, disodium cromoglycate for intestinal issues, and leukotriene receptor antagonists (e.g. montelukast) for bronchial and other mast cell-mediated symptoms. The position paper also addresses emergency preparedness, recommending that all patients be equipped with adrenaline autoinjectors and emergency cards, with specialised emergency passports available through competence networks.⁶⁷

The US National Comprehensive Cancer Network (NCCN) Guidelines for SM (Version 3) recommend that management of mast cell activation symptoms with anti-mediator drug therapy is recommended for symptomatic ISM.⁶⁸ For symptomatic ISM, avapritinib (if platelet counts are $\geq 50 \times 10^9/L$) is listed as a preferred option, while cladribine or peginterferon alfa-2a may be useful in certain circumstances for select patients with severe, refractory mediator symptoms or bone disease not responsive to anti-mediator therapy or bisphosphonates.⁶⁸

Treatments available on the NHS include antihistamines (H1/H2), mast cell stabilisers (such as sodium cromolyn), calcium, bisphosphonates, corticosteroids and adrenaline auto-injector (confirmed by single centre management of ISM at GSTT NHS Centre of Excellence).^{56,65,69} People with ISM are regularly reviewed with respect to symptom burden and mast cell-related comorbidities-DEXA scans (up to 3 times per year).⁵⁶ Notably, a pan-European guideline by the ECNM-AIM (2022) recommended the use of avapritinib and midostaurin in specific ISM cases insufficiently controlled with regards to mediator-associated symptoms.⁵⁰

1.3.8.2 Clinical management of patients with ISM

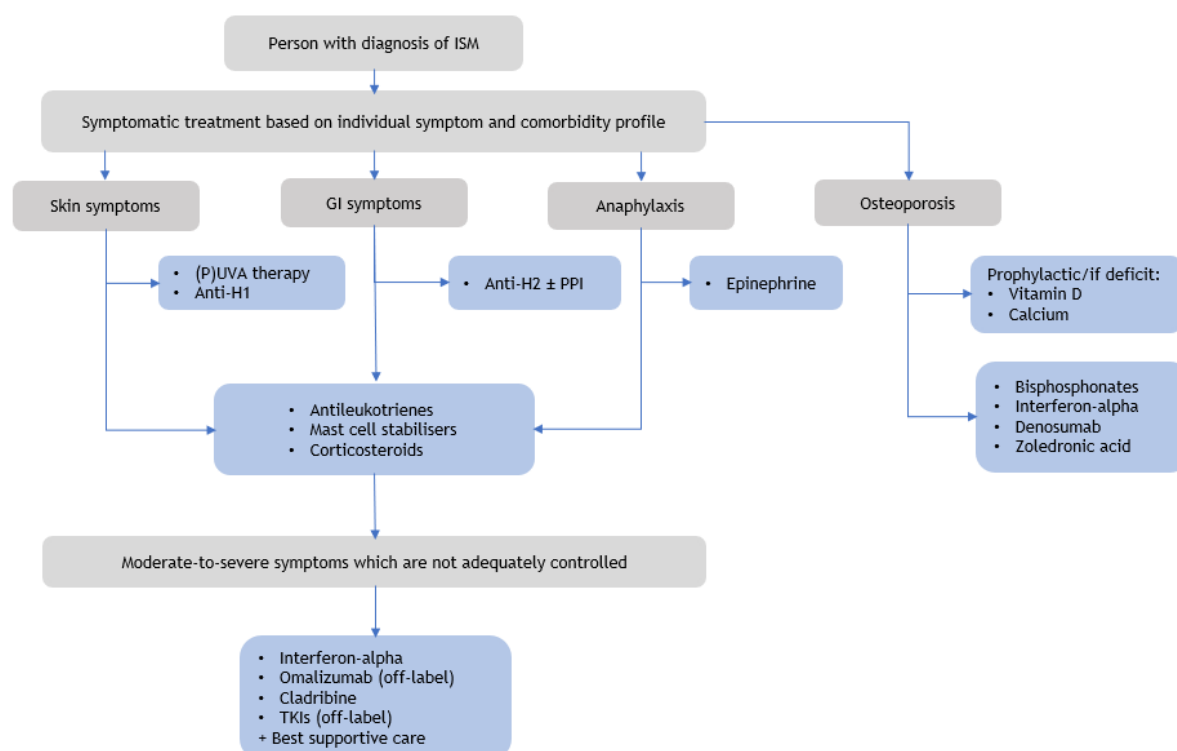
Despite making up the majority of SM cases, there are currently no approved disease-modifying therapies for ISM in England with management focused on symptom control only.⁶⁵ Primary management is focused on symptom and comorbidity control, prevention of anaphylaxis, improvement of patients' QoL and reduction of adverse effects from long-term symptomatic treatments.^{70,71} Without addressing the underlying pathophysiology of ISM, patients may continue to exhibit burdensome symptoms due to inadequate control.^{18,72,73}

1.3.8.2.1 Symptomatic control therapies

Due to the heterogeneous profile of ISM and unpredictable symptoms, patients may receive concurrent symptom-directed therapies including antineoplastic agents and off-label use of TKIs leading to polypharmacy burden (Figure 10).^{15,19} If clinically feasible, treatments may be combined in a stepwise manner in cases of inadequate symptom control.²² People with moderate to severe symptoms, as defined by clinician judgement and objective measures, may not respond to SDT leading to poor QoL and potentially disease progression. Treatment recommendations include interferon-alpha, omalizumab (small proportion of patients with ISM), cladribine and/or TKIs.

Notably, in the European PRISM study, people with ISM patients were treated with H₁ antihistamines (90%), oral corticosteroids (51%), self-injectable epinephrine/adrenaline auto-injector (50%), other topical creams (47%), sodium cromoglycate (41%), H₂ antihistamines (47%), and proton-pump inhibitors (38%).³⁰ Indeed, UK clinical experts from the PRISM study reflected dissatisfaction with currently available options for treating patients with ISM.¹⁵

Figure 10. Treatment pathway and treatment options of patients with ISM



Abbreviations: anti-H1/H2, antihistamines; GI, gastrointestinal; ISM, indolent systemic mastocytosis; PPI, proton-pump inhibitor; P(UVA), psoralen ultraviolet A therapy; TKI, tyrosine kinase inhibitor.

1.3.8.3 NHS England clinical practice

With regards to UK clinical practice, GSTT NHS Trust represents an established centre of excellence for the management of mastocytosis. Through its association with the ECNM network, this site serves to provide state-of-art diagnosis, management and treatment to patients with mast cell disorders, including referred/diagnosed cases of ISM.^{56,69,74}

Multidisciplinary team (MDT) management in this single centre involves haematologists, haematopathologists, dermatologist, immunologist and molecular diagnosticians, aligning with European and US clinical practice.^{50,75} Of 125 patients encountered over a 10-year period, 67% (71/105) of patients biopsied were diagnosed with ISM with a median age of 49 years (range 22-78). Notably, skin involvement was more common in patients with ISM (78%) than AdvSM (54%). Typical symptomatic control treatments employed for these patients include antihistamines, anti-inflammatory agents, anti-leukotriene agents, mast cell stabilising agents, bisphosphonates, proton-pump inhibitors (PPI), psoralen ultraviolet light (PUVA), anti-diarrhoea medication (loperamide)⁴⁴, and

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corticosteroids.⁶⁹ In a more recent symptom burden study (at the same centre), most patients (61%, n=46/76) reported more than 2 prescribed anti-mediator therapies including H1/H2 blockers, PPIs, sodium cromoglycate, montelukast, corticosteroid, bisphosphonates and omalizumab.⁵⁶ Recently, 1 clinical expert (consultant haematologist) validated SDT treatment distribution in UK clinical practice (Table 6) as part of assessing the robustness of the cost-effectiveness model (CEM).⁴⁴

Table 6. Symptom-directed treatment distribution in UK clinical practice

Current SDT management	Percentage of patients given treatment (%)
Anti-H1: Cetirizine	100.0%
Anti-H2 blocker: Ranitidine	66.0%
PPI: Omeprazole	28.2%
Leukotriene inhibitor: Montelukast	35.2%
Corticosteroids: Prednisolone	9.9%
Cromolyn sodium: Nalcrom	35.2%
Loperamide	10-15%
Monoclonal antibodies: Omalizumab	<5%

Abbreviations: anti-H1/-H2, antihistamines; PPI, proton-pump inhibitor; SDT, symptom-directed therapy.

Source: Blueprint Medicines Corporation Clinical expert opinion report.⁴⁴

1.3.8.4 Unmet need in the treatment of ISM

ISM lacks effective standard of care with current therapies offering limited disease control to adequately manage symptoms and often resulting in adverse events and complications. As stated previously, no approved disease-modifying agents are available on the NHS which targets the underlying *KIT D816V* mutation present in approximately 95% of ISM cases as a molecular driver of this disease.²²

SDT management of patients with ISM including prescriptive and non-prescriptive medications (as discussed in Section 1.3.8). Typically, patients are managed long-term with these suboptimal options potentially leading to polypharmacy and treatment-related drug interactions and side effects.⁴⁹ Currently, when these initial treatments fail to alleviate symptom burden, other off-label therapies are administered such as midostaurin, interferon, cladribine and omalizumab.^{22,29,64} NICE recommends reimbursement of midostaurin for the treatment of AdvSM, not ISM. Midostaurin, a multi-kinase inhibitor, exhibits relatively lower *in vitro* activity against the *KITD816V* mutation compared to the highly selective inhibitor avapritinib. This coupled with preliminary clinical evaluation in ISM, which resulted in a high rate

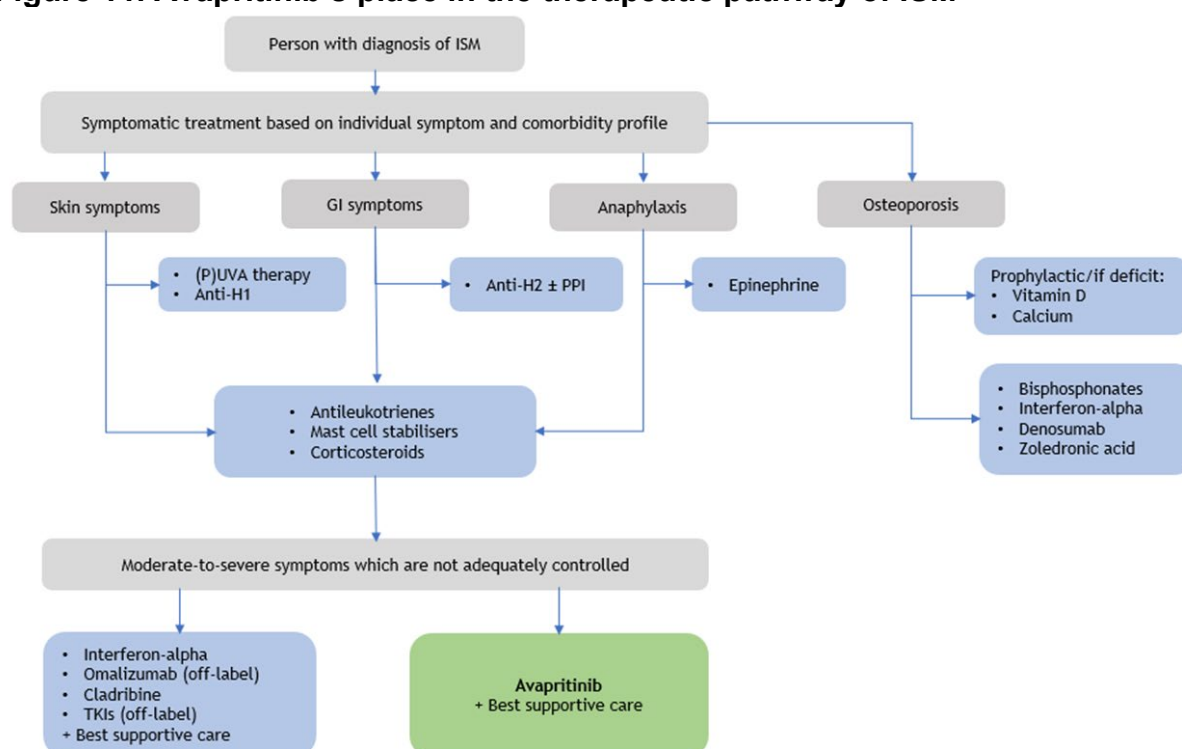
of discontinuations and dose reductions, highlights the inadequacy of off-label therapy with midostaurin.^{76,77}

ISM-SAF measurements in various studies demonstrated a majority of patients with moderate to severe symptoms (TSS $\geq$ 28) with corresponding detrimental impacts on HRQoL, ability to work and activities of daily living.^{15,18,19,49} Increased HCRU and polypharmacy are commonplace with multiple medications per patient especially as symptomatic control measures fail.^{15,49} This highlights the high unmet need for effective and better tolerated treatment options for people living with ISM.

1.3.8.5 Therapeutic positioning of avapritinib in the treatment pathway

With the lack of disease-modifying treatments for ISM and the suboptimal SDT (including in some cases additional treatments with off-label TKIs as well as cytoreductive therapies), there is a distinct unmet need in people with moderate to severe symptoms which are not adequately controlled. Avapritinib, already recommended by NICE for AdvSM¹¹, targets *KIT D816V* mutation thus directly impacting the underlying pathophysiology of ISM.^{6,7,78} As per Figure 11, avapritinib (in addition to SDT) represents a viable treatment option for people living with ISM who have moderate to severe persistent symptoms despite symptom-directed management.

Figure 11. Avapritinib's place in the therapeutic pathway of ISM



Abbreviations: Anti-H1/2; antihistamines; GI, gastrointestinal; ISM, indolent systemic mastocytosis; PPI, proton-pump inhibitors; (P)UVA, psoralen and ultraviolet radiation.

1.4 Equality considerations

Avapritinib use in people living with ISM, as per its clinical development programme and use in the European Union (as per EMA regulatory approval)⁹ has highlighted no apparent equality considerations relevant for this submission.

B2 Clinical effectiveness

2.1 List of relevant clinical effectiveness evidence

Phase 2 PIONEER clinical trial (NCT03731260) is the pivotal study for avapritinib treatment of adults with ISM exhibiting moderate to severe symptoms that were inadequately controlled with symptom-directed therapy (SDT).²⁶ This multi-part trial consists of dose escalation (Part 1), randomised double-blind treatment (Part 2) and an ongoing open-label extension (OLE) (Part 3).

Table 7. Overview of clinical effectiveness evidence

Study	PIONEER (NCT03731260)
Study design	- Phase 2, 3-part, randomised, double-blind, placebo-controlled study: - Part 1: dose selection (25mg, 50mg, 100mg avapritinib vs placebo) - Part 2: randomised efficacy and safety comparison of selected 25mg dose vs placebo (2:1 ratio) - Part 3: OLE Phase for up to 5 years inclusive of time on Parts 1 or 2.
Population	- Adults (≥18 years) - Centrally confirmed WHO diagnosis of ISM with moderate to severe symptoms (ISM-SAF total symptom score ≥ 28) despite optimised symptom-directed therapy with ≥ 2 agents (H1/H2 blockers, leukotriene inhibitors, cromolyn sodium, corticosteroids or omalizumab).
Intervention(s)	- Part 1: Avapritinib 25mg, 50mg, or 100mg orally QD plus SDT - Part 2, Part 3: Avapritinib 25mg orally QD plus SDT
Comparator(s)	- Part 1, Part 2: Matching placebo orally QD plus SDT - Part 3: None (single-arm OLE)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Study	PIONEER (NCT03731260)
Reported outcomes specified in the decision problem	• Symptom severity • Mast cell burden • Response rate • Adverse effects of treatment • Health-related quality of life • Mortality
All other reported outcomes	• Bone health • Anaphylaxis events • Symptomatic treatment usage

Abbreviations: H1, histamine type 1; H2, histamine type 2; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; NA, not applicable; OLE, open-label extension; QD, once daily; SDT, symptom-directed therapy; WHO, World Health Organisation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

2.2 Identification and selection of relevant studies

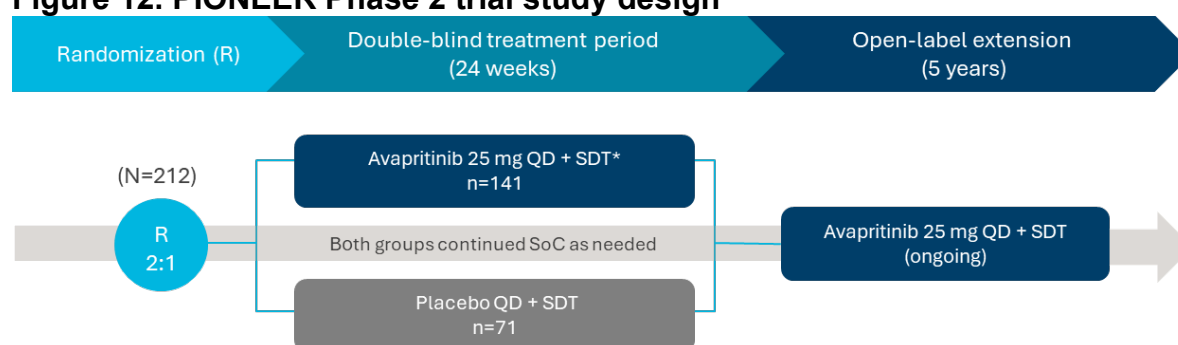
Clinical evidence was identified and selected through a systematic literature review. Searches were conducted in Medline, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials on July 28th 2025. In total, 47 publications were included in the review including 11 relevant publications identified from the grey literature search of HTA websites, clinical trials registries and the proceedings of 22 conferences. Studies with multiple associated publications (such as primary results papers and subsequent subgroup or follow-up analyses) were grouped together and counted as a single study. Hence, the evidence comprised 4 randomised controlled trials (RCTs) from 32 publications, 3 single-arm studies from 5 publications and 9 observational studies from 10 publications. See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.4 Summary of methodology of the relevant clinical effectiveness evidence

2.4.1 PIONEER trial design and characteristics

PIONEER (NCT03731260) was a Phase 2, 3-part randomised, double-blind, placebo-controlled study to evaluate avapritinib once daily (QD) treatment in patients with ISM.²⁶ The design included a sequential approach with Part 1 as a dose escalation phase to establish the recommended Phase 2 dose (RP2D). Part 2 was the pivotal randomised, double-blind, placebo-controlled trial with a 2:1 randomisation ratio (avapritinib). Part 3 was an OLE phase to assess long-term safety and efficacy of avapritinib. The trial incorporated a screening period (up to 8 weeks) that included a 2-week symptom assessment period, and stratification was implemented based on serum tryptase levels at screening (< 20 ng/mL vs ≥ 20 ng/mL). The PIONEER study design is summarised in Figure 12.^{31,54}

Figure 12. PIONEER Phase 2 trial study design



Abbreviations: Indolent Systemic Mastocytosis; ISM-SAF, ISM-Symptom Assessment Form; QD, once daily; SDT, symptom-directed therapy.

Note: *The recommended dose of avapritinib for the double-blind period and open-label extension was identified in Part 1 of PIONEER

Source: Adapted from Blueprint Medicines PIONEER Clinical Study Report, 2022⁵⁴ and Gotlib et al. 2023³¹

2.4.3 Study methodology

2.4.3.1 Eligibility criteria

Key inclusion criteria for PIONEER trial included:⁵⁴

- Adults aged ≥ 18 years with centrally confirmed WHO diagnosis of ISM
- Moderate to severe symptoms based on minimum mean TSS of ≥ 28 on the ISM-Symptom Assessment Form (ISM-SAF) over a 14-day eligibility screening period
- Inadequate symptom control for ≥ 1 baseline symptoms despite optimised therapy with ≥ 2 symptom-directed treatments
- For participants receiving corticosteroids, stable dose of ≤ 20 mg/day prednisone or equivalent for ≥ 14 days prior to screening
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

Key exclusion criteria for the PIONEER trial included:

- Diagnosis of other WHO SM subclassifications (cutaneous mastocytosis, smouldering SM, SM with associated haematological neoplasm, aggressive SM, mast cell leukaemia or mast cell sarcoma)
- Prior treatment with avapritinib
- Recent cytoreductive therapy (< 14 days or 5 half-lives, whichever longer)
- Recent radiotherapy or psoralen ultraviolet A therapy (< 14 days)
- Haematopoietic growth factor use within 14 days before eligibility assessment
- QT interval corrected using Fridericia's formula (QTcF) > 480 msec

2.4.3.2 Study endpoints

*The primary endpoints across the PIONEER study included:*⁵⁴

- Part 1: Determination of the recommended Phase 2 dose (RP2D) of avapritinib
- Part 2: Mean change in ISM-SAF TSS from baseline to week 24
- Part 3: Change from baseline in ISM-SAF TSS through up to 3 years, including proportions with $\geq 30\%$ and $\geq 50\%$ reductions

Key secondary endpoints for Part 2 included:

- Proportion of participants with $\geq 50\%$ reduction in serum tryptase from baseline to week 24

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- Proportion of participants with $\geq 50\%$ reduction in peripheral blood *KIT D816V* VAF or undetectable ($< 0.02\%$) at week 24
- Proportion of participants achieving $\geq 50\%$ reduction in ISM-SAF TSS at Week 24
- Proportion of participants achieving $\geq 30\%$ reduction in ISM-SAF TSS at Week 24
- Proportion of participants with $\geq 50\%$ reduction in bone marrow mast cells or elimination of known baseline mast cell aggregates at week 24

Additional secondary endpoints for Part 2/3, assessed at various timepoints up to 3 years, included:

- Change from baseline in serum tryptase levels
- Change from baseline in *KIT D816V* VAF
- Additional secondary endpoints included changes in quality of life measures (Mastocytosis Quality of Life questionnaire [MC-QoL]; 12-item Short Form Health Survey [SF-12]; Patient Global Impression of Severity [PGIS]; Patient Global Impression of Change [PGIC]; EuroQoL 5-Dimension 5-Level questionnaire [EQ-5D-5L]), changes in SDT medication usage, changes in domain-specific symptom scores, and safety parameters.

2.4.3.3 Protocol amendments

The original protocol, dated 15 February 2018, was amended a total of 10 times. The latest global protocol amendment for the study was dated 07 June 2022 and the study methodology presented is in accordance with this amendment. Key modifications included establishing the eligibility threshold of symptom severity (ISM-SAF TSS) ≥ 28 over the 14-day screening period and setting the recommended Phase 2 dose as 25 mg once daily based on Part 1 findings. A clinically important response was defined as $\geq 30\%$ reduction in TSS from baseline.⁵⁴

The primary endpoint for Part 2 was changed from percentage based to mean change in ISM-SAF TSS from baseline to Week 24 compared to placebo. Secondary endpoints were expanded to include both moderate ($\geq 30\%$ reduction in ISM-SAF TSS) and substantial ($\geq 50\%$ reduction in ISM-SAF TSS) symptom improvements and objective measures of disease burden ($\geq 50\%$ reduction in serum tryptase and $\geq 50\%$ reduction in *KIT D816V* VAF). The study population in Part 2 was refined to focus on people with ISM only, and the statistical analysis method was updated to

analysis of covariance (ANCOVA) accounting for randomisation stratification factors (serum tryptase levels and baseline symptom severity).⁵⁴

Amendment 12 (dated 20 July 2023) established post-treatment cessation follow-up procedures, enabling long-term monitoring of objective disease measures and patient outcomes for up to 2 years after treatment discontinuation through regular telephone assessments and optional central laboratory review of local samples.⁷⁹

These amendments were implemented to refine the study design and endpoints based on evolving clinical evidence and regulatory guidance, while maintaining study integrity.

An overview of the PIONEER study methodology is presented in Table 8.

Table 8. Overview of PIONEER Phase 2 study methodology

Trial number (acronym)	NCT03731260 (PIONEER)
Trial design	Multicentre, three-part Phase 2 study: • [Part 1] Dose escalation • [Part 2] Pivotal, double-blind, placebo-controlled RCT • [Part 3] Long-term open-label extension.
Eligibility criteria for participants (Key Inclusion)	• Adult male and female participants • Centrally confirmed WHO diagnosis of ISM • Moderate to severe symptoms according to a minimum mean ISM-SAF TSS of ≥ 28 over a 14 day screening period • <i>KIT D816V</i> mutation positive
Eligibility criteria for participants (Key Exclusion)	• A diagnosis of mastocytosis other than ISM • Prior treatment with avapritinib and/or antineoplastic therapy within 28 days or tyrosine kinase inhibitor therapy within 14 days before the TSS eligibility assessment
Settings and locations where the data were collected	• 42 sites, majority located in Europe (n=23), with 19 located in North America
Trial drugs Intervention(s) (n=[x]) and comparator(s) (n=[x])	Part 1: • Intervention: avapritinib orally once daily at one of 3 dose levels: 25 mg (n=10), 50 mg (n=10), or 100 mg (n=10) • Comparator: Placebo + SDT (n=9) Part 2: • Intervention: Avapritinib 25 mg orally once daily + SDT (n=141) • Comparator: Placebo + SDT (n=71)

Trial number (acronym)	NCT03731260 (PIONEER)
	- Based on Part 1 results, 25 mg avapritinib was selected as the recommended Phase 2 dose (RP2D) Part 3: - Intervention: Avapritinib 25 mg daily - Dose escalation to 50 mg avapritinib was permitted based on prespecified clinical criteria
Permitted and disallowed concomitant medication	- Participants received SDT according to treating physician's discretion - All participants were treated with at least 2 current or prior SDT medications (per inclusion criteria) - Most common SDTs: antihistamines for systemic use (97.2% in avapritinib group, 100% in placebo group) and drugs for peptic ulcer and gastro-oesophageal reflux disease (73.8% in avapritinib group, 78.9% in placebo group)
Primary endpoints (including scoring methods and timings of assessments)	- Part 1: The RP2D in participants with ISM (12 weeks of treatment) - Part 2: Mean change in TSS of the ISM-SAF from baseline to Week 24 - Part 3: The long-term safety and efficacy of avapritinib (5 years)
Other endpoints used in the economic model/specified in the scope	≥ 30% and ≥ 50% reduction in TSS from baseline at Week 24 - EQ-5D utility values by disease severity category derived from PIONEER trial and PRISM study - Health state distribution by TSS severity categories during initial treatment period (6 cycles) and maintenance phase - Treatment-related adverse event incidence rates - Patient distribution across mild (TSS 0-27), moderate (TSS 28-41), and severe (TSS 42-110) health states
Further secondary and exploratory endpoints	- Change in measures of mast cell burden - Change in SDT usage - Change in gastrointestinal and skin domains, neurocognitive symptom cluster, and individual symptom scores of ISM-SAF - Change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score of ISM-SAF - Safety and tolerability (AEs, vital signs, ECGs, lab tests) - Pharmacokinetics and correlations between exposure and endpoints - Changes in quality of life measures (MC-QoL, SF-12, PGIS, PGIC; EQ-5D-5L)

Trial number (acronym)	NCT03731260 (PIONEER)
Pre-planned subgroups	• Baseline serum tryptase levels (< 20 ng/mL vs ≥ 20 ng/mL) • Gender (male/female) • Age group (< 65/≥ 65 years) • Region (North America/Europe) • Baseline ISM severity (moderate/severe) • ECOG status • Prior TKI therapy
Duration of follow-up / loss to follow-up / cross-over	• Part 2: 24 weeks (6 cycles) of treatment • Part 3: Open-label extension up to 5 years (ongoing) • Cross-over: After Part 2, participants from both avapritinib and placebo groups could continue/switch to 25 mg avapritinib QD in Part 3 • Loss to follow-up in Part 2: 5 participants discontinued from each treatment group (avapritinib or placebo) • By Part 3 data cut-off (DCO, February 21, 2025): [REDACTED] participants discontinued, [REDACTED] participants ongoing in Part 3

Abbreviations: AEs, adverse events; ECGs, electrocardiograms; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL 5-Dimension 5-Level questionnaire; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MC-QoL, Mastocytosis Quality of Life questionnaire; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; QD, once daily; RCT, randomised controlled trial; RP2D, recommended Phase 2 dose; SDT, symptom-directed therapy; SF-12, 12-item Short Form Health Survey; TKI, tyrosine kinase inhibitor; TSS, total symptom score; WHO, World Health Organisation.

Sources: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Blueprint Medicines Corporation PIONEER Clinical Study Report (2025)⁸⁰; Triggiani et al., 2024⁸¹

2.4.4 PIONEER patient disposition and demographics

Baseline demographic and clinical characteristics were generally similar and well-balanced between treatment groups across all parts of the PIONEER trial. All enrolled participants had significant symptom burden as measured by ISM-SAF TSS, which was required for study eligibility (see 2.4.3.1).⁵⁴

Protocol deviations in the PIONEER trial were documented across all study parts. In Part 1 of the study, the most common major protocol deviation was related to informed consent. For Part 2, a higher proportion of participants in the avapritinib 25 mg group ([REDACTED]) compared to the placebo group ([REDACTED]) had at least one major protocol deviation. The most frequent deviation in Part 2 was related to ISM-SAF compliance, defined as fewer than [REDACTED] completed daily scores in a cycle. The frequency of this deviation was low, reported at 10 participants ([REDACTED] of n=[REDACTED]) in the 25 mg avapritinib group and 3 participants ([REDACTED] of n=[REDACTED]) in the placebo group.

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Additionally, some participants had deviations related to dosing compliance below [REDACTED] and the administration of prohibited concomitant medications, although some of these were later deemed minor. None of the major protocol deviations were thought to impact the integrity of the data.⁵⁴

The most common reasons for discontinuation across Parts 1, 2, and 3 were withdrawal of consent ([REDACTED] in intention-to-treat (ITT) population, [REDACTED] in Per-Protocol population), followed by adverse events ([REDACTED] in ITT population, [REDACTED] in Per-Protocol population), and other reasons including progressive disease, investigator decision, non-compliance, pregnancy, lost to follow-up, and death unrelated to study drug.⁸⁰

2.4.4.1 Part 1 patient disposition and baseline characteristics

In Part 1, 39 participants were randomised to receive placebo (n=[REDACTED]) or avapritinib at doses of 25 mg (n=[REDACTED]), 50 mg (n=[REDACTED]), or 100 mg (n=[REDACTED]) in combination with SDT. [REDACTED] participants discontinued from Part 1, and 34 participants completed and rolled over to Part 3. Baseline demographics in Part 1 showed a predominance of female ([REDACTED]), younger (<65 years, [REDACTED]), White ([REDACTED]) participants. All participants had significant symptom burden with elevated tryptase levels and a high prevalence of *KIT D816V* mutation (Table 9).⁵⁴

Table 9. Key baseline characteristics in PIONEER Part 1

Parameter	All participants (N=39)
Demographics	
Female, n (%)	[REDACTED]
Age < 65 years, n (%)	[REDACTED]
White, n (%)	[REDACTED]
Not Hispanic or Latino, n (%)	[REDACTED]
Mean (SD) BMI, kg/m ²	[REDACTED]
Disease characteristics	
Mean (SD) ISM-SAF TSS	[REDACTED]
Mean (SD) serum tryptase, ng/mL	[REDACTED]
Participants with bone marrow mast cell aggregates, n (%)	[REDACTED]
<i>KIT D816V</i> mutation detected in peripheral blood, n (%)	[REDACTED]
Mean (SD) <i>KIT D816V</i> allele fraction	[REDACTED]

Abbreviations: BMI, body mass index; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; SD, standard deviation; TSS, Total Symptom Score.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

2.4.4.2 Part 2 patient disposition and baseline characteristics

In Part 2, 212 participants were enrolled: 141 in the 25 mg avapritinib + SDT group and 71 in the placebo + SDT group. Patient disposition was similar between treatment groups, with 5 participants discontinuing from each arm.⁵⁴

Baseline characteristics were well-balanced between treatment arms, with most participants being female (70.9-76.1%), under 65 years (84.5-93.6%), and with similar disease burden (Table 10). Both groups had comparable ISM-SAF TSS scores, serum tryptase levels, *KIT D816V* mutation burden, and bone marrow mast cell infiltration. Medical history was consistent with typical ISM presentation, dominated by gastrointestinal, musculoskeletal, and skin disorders. These baseline characteristics were consistent with the typical ISM patient population.^{31,54}

The majority of participants received SDT medication/therapy at baseline (99.6%). The avapritinib 25 mg + SDT group reported a median of 3.0 concomitant SDT medications per patient (range 0-11) and the placebo + SDT group reported a median of 4.0 concomitant SDT medications per patient (range 1-8).^{31,54}

Table 10. Key baseline characteristics in PIONEER Part 2

Parameter	Avapritinib 25 mg (N=141)	Placebo (N=71)
Demographics		
Female, n (%)	100 (70.9)	54 (76.1)
Age, years, mean (SD)	48.7 (11.70)	52.2 (12.52)
Age < 65 years, n (%)	132 (93.6)	60 (84.5)
White, n (%)	109 (77.3)	61 (85.9)
Not Hispanic or Latino, n (%)	99 (70.2)	58 (81.7)
Weight, kg, mean (SD)	81.12 (17.92)	82.19 (17.80)
BMI, kg/m ² , mean (SD)	28.31 (5.4)	29.46 (5.28)
Disease characteristics		
Mean (SD) ISM-SAF TSS	50.17 (19.15)	52.43 (19.82)
ISM-SAF TSS ≥ 42 (severe), n (%)	87 (61.7)	45 (63.4)
Median (min, max) serum tryptase, ng/mL	38.40 (3.6, 256.0)	43.70 (5.7, 501.6)
Median (min, max) <i>KIT</i> D816V MAF	0.39 (0.00, 41.29)	0.26 (0.00, 36.74)
Median (Min, Max) bone marrow mast cells, %	7.00 (1.0, 50.0)	7.00 (1.0, 70.0)
Median (min, max) mast cells in skin (lesional), count/mm ²	459.0 (89, 2870)	617.5 (83, 2609)
Most common medical history, n (%)		
Gastrointestinal disorders	114 (80.9)	55 (77.5)
Musculoskeletal and connective tissue disorders	112 (79.4)	58 (81.7)
Skin and subcutaneous tissue disorders	110 (78.0)	52 (73.2)

Abbreviations: BMI, body mass index; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MAF, mutant allele fraction; Max, maximum; Min, minimum; SD, standard deviation; TSS, Total Symptom Score.

Sources: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Gotlib et al. 2023³¹

2.4.4.3 Part 3 patient disposition and baseline characteristics

Overall, in the ITT population, 34 participants from Part 1 and 201 participants from Part 2 rolled over into Part 3 of PIONEER. As of the data cut-off (DCO; February 21, 2025), ■ participants have completed Part 3, with these patients either transitioning to commercially available avapritinib (if possible), enrolling in a rollover study or discontinuing treatment. Additionally, ■ participants remained in Part 3, and ■ participants had discontinued in Part 3.⁸⁰ For overall patient flow throughout the PIONEER study, refer to Appendix B for a summary CONSORT diagram from initial screening period to the latest DCO.

When considering only the Per-Protocol population from the Part 1 and 2 of the PIONEER (N=220), [REDACTED] participants rolled over into Part 3, including [REDACTED] from Part 1 and [REDACTED] from Part 2. The [REDACTED] participants who discontinued from the Per-Protocol population in Parts 1 or 2, did so before rolling over to Part 3. As of the DCO, [REDACTED] participants had completed Part 3, [REDACTED] participants remained in Part 3, and [REDACTED] participants had discontinued the study in Part 3. A summary of baseline characteristics for participants in the safety and per-protocol populations in Part 3 is provided in Table 11.^{80, 80}

In total, [REDACTED] participants who initiated avapritinib at any dose have undergone protocol-defined dose escalation to 50 mg in Part 3 of PIONEER, including [REDACTED] participants who started treatment with a 25-mg dose. Of the [REDACTED] participants with dose escalation, [REDACTED] have completed Part 3, and a total of [REDACTED] participants have discontinued treatment due to withdrawal of consent (n=[REDACTED]), investigator decision (n=[REDACTED]), progressive disease (n=[REDACTED]), pregnancy and other.

Table 11. Key baseline characteristics in PIONEER Part 3

Parameter	Safety population		Per-protocol population	
	Avapritinib starting dose 25-mg (N=████)	Avapritinib all starting doses (N=████)	Avapritinib 25-mg starting dose (N=████)	Avapritinib all starting doses (N=████)
Demographics				
Female, n (%)	████████	████████	████████	████████
Age, years, mean (SD)	████████	████████	████████	████████
Age < 65 years, n (%)	████████	████████	████████	████████
White, n (%)	████████	████████	████████	████████
Not Hispanic or Latino, n (%)	████████	████████	████████	████████
Mean (SD) BMI, kg/m ²	████████	████████	████████	████████
Disease characteristics				
Mean (SD) ISM-SAF TSS	████████	████████	████████	████████
Median (range) serum tryptase, ng/mL	████████	████████	████████	████████
Median (range) <i>KIT</i> D816V VAF, %	████████	████████	████████	████████

*For the dose escalation population, baseline values are defined as the last value prior to dose escalation to 50 mg.
Abbreviations: BMI, body mass index; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; SD, standard deviation; TSS, Total Symptom Score; VAF, variant allele frequency.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

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

2.5.1 Analysis populations

The trial evaluated 6 distinct analysis populations (ITT, per-protocol, safety, dose escalation, long-term and overall) as detailed in Table 12.^{54,80}

The overall analysis population included participants who received avapritinib at any point in the study, with analyses using the avapritinib baseline (last observation prior to first avapritinib dose in any part).^{54,80}

Refer to Appendix B for details regarding patient eligibility and patient flow through the PIONEER clinical study.

2.5.2 Statistical analyses

An overview of the statistical analysis plan for the Phase 2 PIONEER study is presented in Table 12. Further detail on subgroup analysis from PIONEER Part 2 is presented in Appendix C.

In Part 1, the primary analysis focused on determining the recommended Phase 2 dose based on mean change in ISM-SAF TSS at Week 12, using descriptive statistics to compare each avapritinib dose group (25 mg, 50 mg, 100 mg QD) to placebo. The 25 mg QD dose was selected based on comparable efficacy to higher doses with improved tolerability.⁵⁴

For Part 2, participants with high-dose steroid use in the 7 days before Week 24 or for more than 14 days consecutively from Week 0 to Week 24 were excluded to prevent confounding. A one-sided p-value of <0.025 was required to demonstrate the superiority of the avapritinib + SDT arm in reducing symptoms vs. placebo + SDT. The primary efficacy analysis was conducted in the ITT population.⁵⁴ The PP population was used for sensitivity analyses.⁵⁴

For Part 3, which included participants who rolled over from both Part 1 and Part 2 of the study, long-term safety and efficacy of avapritinib was evaluated using descriptive statistics.⁸⁰

Table 12. Overview of statistical analysis in PIONEER Phase 2 efficacy findings

Trial number (acronym)	NCT03731260 (PIONEER)
Study hypotheses	• Primary hypothesis: Avapritinib 25 mg + SDT once daily is superior to placebo + SDT in reducing ISM symptoms as measured by mean change in ISM-SAF TSS from baseline to Week 24. • Secondary hypotheses: Avapritinib + SDT is superior to placebo + SDT in reducing mast cell burden (serum tryptase, <i>KIT D816V</i> VAF, bone marrow mast cells) and achieving clinically meaningful symptom reductions ($\geq 30\%$ and $\geq 50\%$ in TSS).
Analysis sets	ITT population: All randomised participants (primary efficacy analyses). • Part 1: n=39 (25 mg: n=■; 50 mg: n=■; 100 mg: n=■; placebo: n=■) • Part 2: n=212 (25 mg: n=141; placebo: n=71) PP population: ITT participants without major protocol deviations (sensitivity analyses). • Part 2: n=190 (25 mg: n=123; placebo: n=67) • Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■) Safety population: All participants who received ≥ 1 dose of study drug (safety analyses). • Part 1: n=39 (25 mg: n=■; 50 mg: n=■; 100 mg: n=■; placebo: n=■) • Part 2: n=212 (25 mg: n=141; placebo: n=71) • Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■) Dose escalation population: Participants who underwent protocol-defined dose escalation to 50 mg in Part 3. • Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■)
Sample size, power calculation	For Part 2, approximately 204 participants provided $> 90\%$ power to detect a mean change of TSS of -10 in the placebo + SDT group versus -19.7 in the avapritinib + SDT group, assuming a SD of 20 and using a one-sided type I error rate of 0.025 with a two-sample t-test.
Statistical analysis	• Primary endpoint (Part 2): ANCOVA for mean change in ISM-SAF TSS from baseline to Week 24, controlling for randomisation stratification factors (serum tryptase < 20 vs ≥ 20 ng/mL and baseline ISM severity [moderate vs severe]). One-sided p-value < 0.025 defined statistical significance. • Key secondary endpoints (Part 2): Tested hierarchically using a gatekeeping procedure to control family-wise Type I error at 0.025. The Cochran-Mantel-Haenszel test was used

Trial number (acronym)	NCT03731260 (PIONEER)
	for binary endpoints, controlling for the same stratification factors. • Descriptive statistics: Mean, standard deviation, median, minimum, and maximum for continuous variables; frequencies and percentages for categorical variables.
Efficacy analysis	• Subgroup analyses: Included analyses by baseline tryptase level (< 20 vs ≥ 20 ng/mL), baseline TSS severity (moderate vs severe), age, sex, and geographic region. • Sensitivity analyses: PP analysis and alternative approaches to missing data handling to assess robustness of primary findings. • Open-label extension: Part 3 baseline definitions varied by patient treatment history: for participants who received avapritinib in Parts 1 or 2, baseline was the time of avapritinib initiation; for participants who received placebo in Parts 1 or 2, baseline was defined as the start of Part 3. For dose escalation analysis, baseline was defined as the last value prior to dose escalation to 50 mg.
Data management, patient withdrawals	• Participants could withdraw from the study at any time. Participants who discontinued treatment were encouraged to complete all remaining scheduled visits. • For participants who discontinued treatment or withdrew from the study, all available data up to the point of discontinuation were included in analyses. • Missing data approach: If a patient was missing > 7 days of scores in the 14 days before baseline or Week 24, the respective score was considered missing. • Participants with high-dose steroid use within 7 days before Week 24 or > 14 consecutive days at any point from baseline to Week 24 were excluded from the primary efficacy analysis. • No imputation was performed for the primary analysis; sensitivity analyses used various approaches to assess the impact of missing data.

Abbreviations: ANCOVA, analysis of covariance; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, intent-to-treat; OLE, open-label extension; PP, per-protocol; TSS, total symptom score; VAF, variant allele frequency.

Sources: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.6 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for the pivotal Phase 2 trial PIONEER is presented in Appendix B.

2.7 Clinical effectiveness results of the relevant studies

The Phase 2 PIONEER study is the clinical study supporting this submission and, as such, results from Part 1 (dose escalation), Part 2 (randomised, double-blinded, placebo-controlled trial) and Part 3 (ongoing OLE) of this study are presented throughout the clinical effectiveness section.

2.7.1 PIONEER preliminary findings: Recommended Phase 2 dose

Part 1 of PIONEER assessed 3 avapritinib dose levels (25 mg, 50 mg and 100 mg once daily) versus placebo in participants with ISM, with [REDACTED] participants per active dose and [REDACTED] in placebo. The 100 mg dose demonstrated the fastest symptom reduction at Week 12, but plateaued thereafter. By Week 24, the 25 mg and 50 mg doses achieved comparable reductions as outlined in Table 13 and Table 14. Based on Part 1 results, 25 mg avapritinib once daily was selected as the RP2D for subsequent study parts.⁵⁴

Table 13. Mean change in ISM-SAF TSS from baseline to Week 24 (PIONEER Part 1 ITT Population)

Parameter, mean (SD)	Placebo N=[REDACTED]	25 mg QD N=[REDACTED]	50 mg QD N=[REDACTED]	100 mg QD N=[REDACTED]
Baseline	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Week 12 change	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Week 24 change	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, intent-to-treat; QD, once daily; SD, standard deviation; TSS, total symptom score.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

Table 14. Percentage change in mast cell burden measures at Week 12 (PIONEER Part 1 ITT Population)

Measure	Placebo N=■	25 mg QD N=■	50 mg QD N=■	100 mg QD N=■
Serum tryptase (%)	■	■	■	■
Bone marrow mast cells (%)	■	■	■	■
<i>KIT</i> D816V allele fraction (%)	■	■	■	■

Abbreviations: ITT, intent-to-treat; QD, once daily; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

2.7.2 Symptom burden as per ISM-SAF in PIONEER randomised phase

2.7.2.1 Change in overall symptom score (ISM-SAF TSS) from baseline to Week 24: Avapritinib vs placebo

At Week 24 in Part 2, the LS mean (SE) change from baseline in ISM-SAF TSS was -15.58 (1.54) points for avapritinib 25 mg versus -9.15 (2.01) for placebo, demonstrating a statistically significant between-group difference of -6.43 (95% CI: -10.90, -1.96; $p=0.003$), as shown in Table 15. The change in ISM-SAF TSS over time for both treatment groups is presented in Figure 13, which shows an initial reduction in both groups followed by a plateau in the placebo group, while the avapritinib group continued to improve.⁵⁴

A sensitivity analysis using Markov Chain Monte Carlo (MCMC) imputation for missing values was consistent with the primary analysis, showing an LS mean (SE) change of -15.33 (1.54) for avapritinib versus -9.64 (2.02) for placebo (difference: -5.69; 95% CI: -10.16, -1.23; $p=0.006$). Additionally, analysis in the PP population showed similar results with a between-group difference of -7.53 (95% CI: -12.36, -2.70; $p=0.001$).^{31,54}

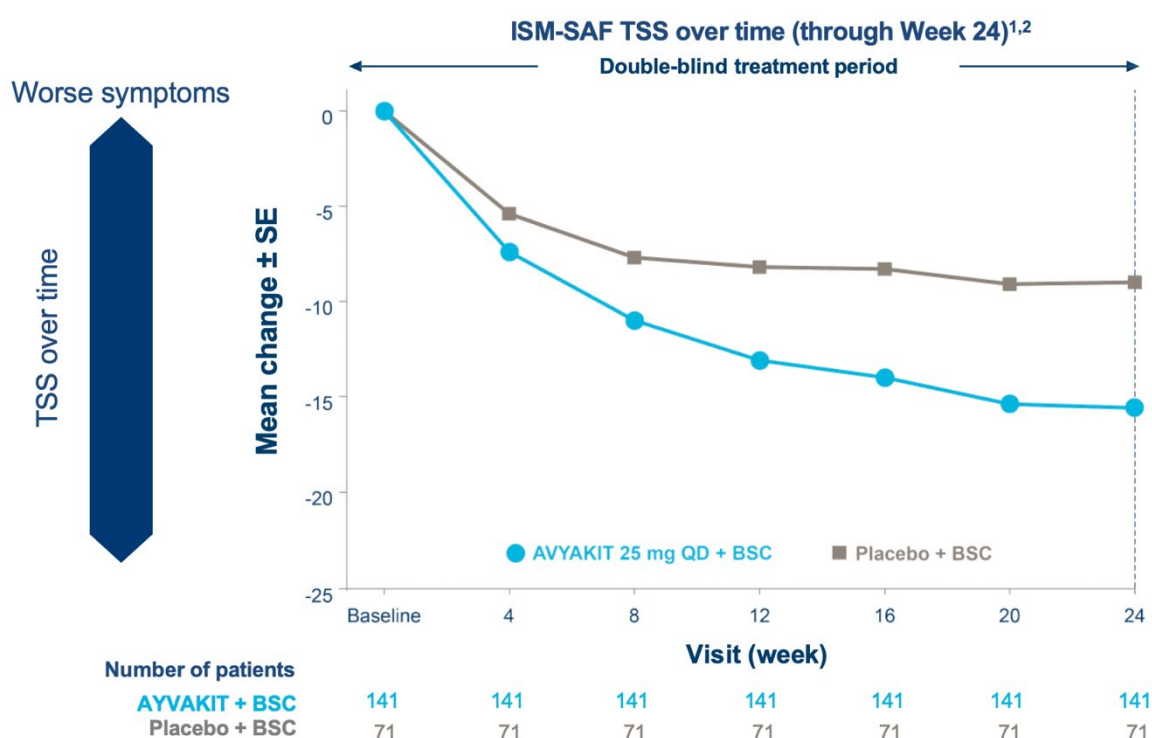
Table 15. Mean change in TSS of ISM-SAF from baseline to Week 24 (PIONEER Part 2 ITT Population)

Parameter	Avapritinib 25 mg (N=141)	Placebo (N=71)
Baseline , Mean (SD)	50.17 (19.15)	52.43 (19.82)
Week 24 , Mean (SD)	33.48 (20.06)	42.32 (21.03)
CFB , LS Mean (SE)	-15.58 (1.54)	-9.15 (2.01)

Abbreviations: CFB, change from baseline; CI, confidence interval; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, intent-to-treat; LS, least squares; SD, standard deviation; SE, standard error; TSS, total symptom score.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

Figure 13. Change from baseline of ISM-SAF TSS at Week 24 (PIONEER Part 2 ITT population)



Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

Abbreviations: BSC, best supportive care; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, Intent-to treat; LS Mean, least squares mean; SDT, symptom-directed therapy; TSS, total symptom score.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

2.7.2.2 Patients with ISM achieving 30% and 50% reductions in TSS at Week 24: Avapritinib vs placebo

A greater proportion of participants in the avapritinib group achieved clinically meaningful reductions (0% and 50%) in TSS at Week 24 compared with placebo, as detailed in Table 16. For the $\geq 50\%$ reduction threshold, 24.8% of avapritinib-treated participants versus 9.9% of placebo participants achieved this level of improvement (odds ratio: 3.10; 95% CI: 1.24, 8.64; $p=0.005$). For the $\geq 30\%$ reduction threshold,

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45.4% of avapritinib-treated participants versus 29.6% of placebo participants achieved this level of improvement (odds ratio: 2.07; 95% CI: 1.08, 3.99; p=0.009). The increase in the percentage of participants achieving $\geq 50\%$ and $\geq 30\%$ reductions in TSS over time is illustrated in Figure 14 and Figure 15, respectively.⁵⁴ Long-term follow-up data from the OLE (Part 3) demonstrated sustained response rates through 3 years of treatment, with placebo patients who crossed over to avapritinib showing increasing response rates beyond 24 weeks (see Section 2.7.7.2).

Sensitivity analyses excluding participants with missing baseline TSS values showed similar results, with [REDACTED] versus [REDACTED] of participants achieving $\geq 50\%$ reduction and [REDACTED] versus [REDACTED] achieving $\geq 30\%$ reduction in avapritinib versus placebo groups, respectively. Further sensitivity analyses excluding participants with missing Week 24 TSS values and those who used high-dose steroids, as well as analyses in the PP population, were also consistent with the primary findings.⁵⁴

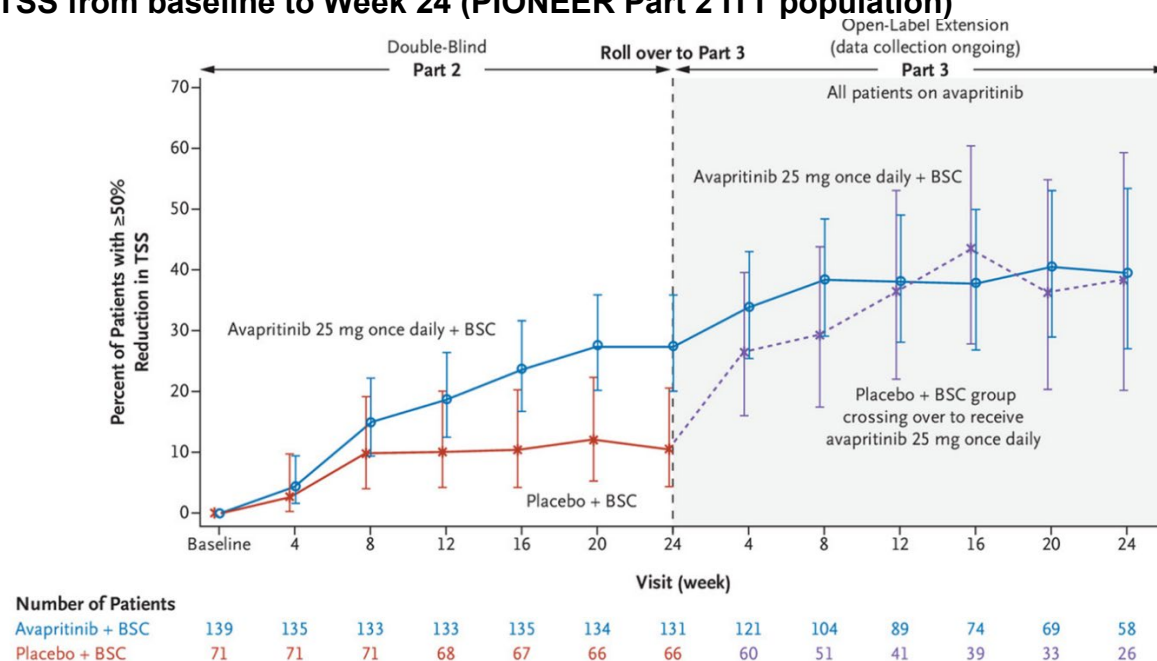
Table 16. Proportion of participants with $\geq 50\%$ and $\geq 30\%$ reduction in ISM-SAF TSS at Week 24 (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg N=141 n/N (%) (95% CIs)	Placebo N=71 n/N (%) (95% CI)	Odds ratio (95% CI)	P-Value
$\geq 50\%$ reduction in TSS	35/141 (24.8) (17.9, 32.8)	7/71 (9.9) (4.1, 19.3)	3.10 (1.24, 8.64)	0.005
$\geq 30\%$ reduction in TSS	64/141 (45.4) (37.0, 54.0)	21/71 (29.6) (19.3, 41.6)	2.07 (1.08, 3.99)	0.009

Abbreviations: CI, confidence interval; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, intent-to-treat; TSS, total symptom score.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

Figure 14. Percentage of participants with $\geq 50\%$ Reduction in the ISM-SAF TSS from baseline to Week 24 (PIONEER Part 2 ITT population)

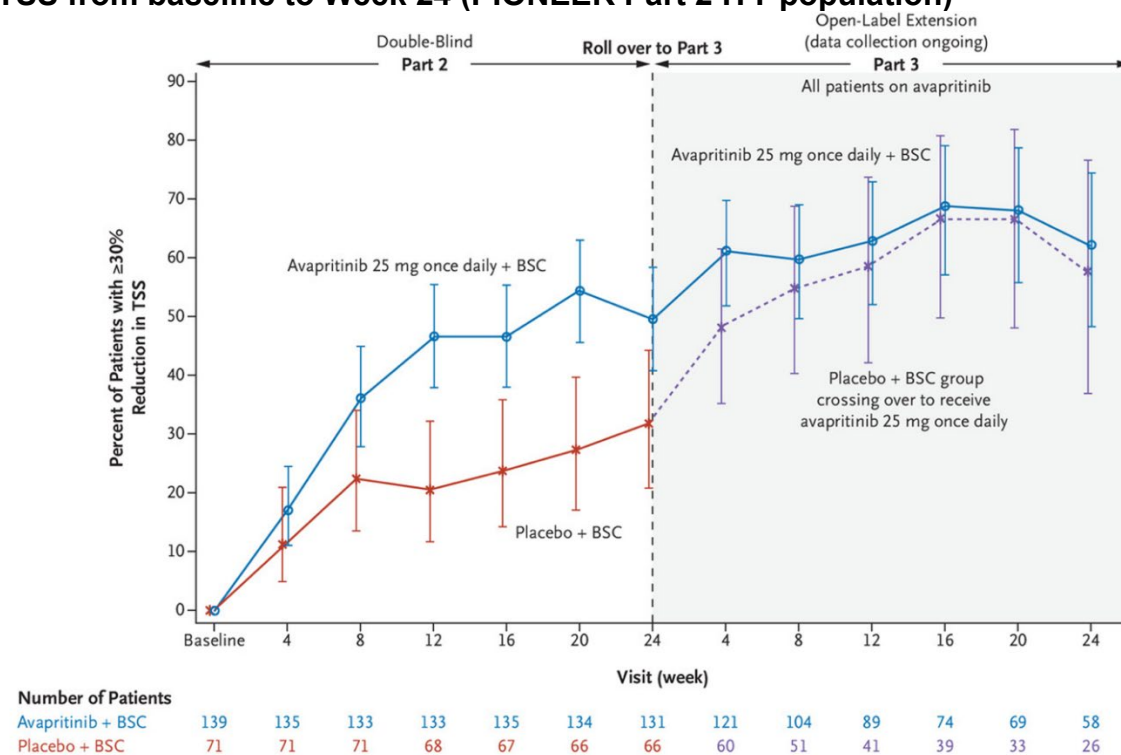


Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

Abbreviations: BSC, best supportive care; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, Intention-to treat; SDT, symptom-directed therapy; TSS, Total Symptom Score.

Source: Gotlib et al. (2023).³¹

Figure 15. Percentage of participants with $\geq 30\%$ Reduction in the ISM-SAF TSS from baseline to Week 24 (PIONEER Part 2 ITT population)



Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

Abbreviations: ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT, Intention-to treat; SDT,

symptom-directed therapy; TSS, Total Symptom Score.
Source: Gotlib et al. (2023).³¹

2.7.2.3 Changes in ISM-SAF domain scores from baseline to Week 24: Avapritinib vs placebo

The ISM-SAF includes individual domains for GI symptoms, skin symptoms and a neurocognitive symptom cluster. As presented in Table 17, at Week 24, the skin domain showed the most pronounced difference between treatment groups with a mean (SD) change from baseline of -5.87 (6.49) for avapritinib versus -2.64 (4.11) for placebo (difference: -3.23; 95% CI: -4.73, -1.73; $p < 0.0001$).⁸² Among individual symptom scores, statistically significant differences favouring avapritinib were observed for spots severity ($p < 0.0001$), itching severity ($p < 0.0001$), and flushing severity ($p = 0.009$) at Week 24.⁵⁴

Table 17. Changes in key domains of ISM-SAF at Week 24 (PIONEER Part 2 ITT Population)

Domain/cluster	Avapritinib 25 mg N=131 Mean (SD) change	Placebo N=66 Mean (SD) change	Difference (95% CI)	p-value
GI domain	-3.74 (4.87)	-3.14 (4.67)	-0.60 (-2.03, 0.83)	0.410
Skin domain	-5.87 (6.49)	-2.64 (4.11)	-3.23 (-4.73, -1.73)	< 0.0001
Neurocognitive symptom cluster	-4.03 (5.22)	-2.81 (4.29)	-1.22 (-2.69, 0.25)	0.102

Abbreviations: CI, confidence interval; GI, gastrointestinal; ITT, intent-to-treat; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Giannetti et al. (2024).⁸²

2.7.3 Objective measures of mast cell burden at Week 24: Avapritinib vs placebo

The proportion of participants who achieved $\geq 50\%$ reduction in objective measures of mast cell burden from baseline to Week 24 were evaluated as key secondary endpoints. These measures included serum tryptase, *KIT D816V* MAF and bone marrow mast cells.

Mean changes showed significant reductions with avapritinib versus placebo for serum tryptase, *KIT D816V* MAF and bone marrow mast cells. The proportion of

participants achieving $\geq 50\%$ reduction was significantly higher with avapritinib across all measures ($p < 0.0001$ for all comparisons).

Post-hoc analyses showed that among participants with baseline tryptase ≥ 20 ng/mL, over half of avapritinib-treated participants achieved normalisation, with approximately half of these reaching levels below detection limits. Similarly, [REDACTED] of avapritinib participants with bone marrow aggregates at baseline had no aggregates at Week 24. For *KIT D816V*, [REDACTED] of participants with baseline MAF $\geq 1\%$ achieved reduction to $< 1\%$ with avapritinib, while no placebo participants reached this threshold.

These findings are summarised in Table 18 were consistent across sensitivity analyses in the PP population.⁵⁴

Table 18. Objective measures of mast cell burden at Week 24 (PIONEER Part 2 ITT Population)

Parameter	Avapritinib 25 mg N=141	Placebo N=71	Difference/ Odds Ratio (95% CI)	P-Value
Mean (SD) change from baseline				
Serum tryptase (ng/mL)			-	-
KIT D816V MAF (%)			-	-
Bone marrow mast cells (%)			-	-
Response rates: n/N (%) (95% CI)				
≥ 50% reduction in serum tryptase	76/141 (53.9) (45.3, 62.3)	0/71 (0.0) (0.0, 5.1)	OR: NE (30.59, NE)	<0.0001
≥ 50% reduction in KIT D816V MAF or undetectable	80/118 (67.8) (58.6, 76.1)	4/63 (6.3) (1.8, 15.5)	OR: 39.34 (10.93, 140.56)	<0.0001
≥ 50% reduction in bone marrow mast cells or no aggregates	56/106 (52.8) (42.9, 62.6)	13/57 (22.8) (12.7, 35.8)	OR: 4.74 (2.06, 11.45)	<0.0001
Post-hoc analyses: nn (%)				
Normalisation of tryptase (< 20 ng/mL)	58/107 (54.0)	1/50 (2.0)	-	-
Tryptase below LLD (< 11.4 ng/mL)	29/107 (27.1)	0/50 (0.0)	-	-
Undetectable KIT D816V MAF (< 0.02%)	12/109 (11.0)	3/54 (6.0)	-	-
Reduction to KIT D816V MAF < 1%	14/40 (35.0)	0/22 (0.0)	-	-
No bone marrow mast cell aggregates	33/91 (36.0)	6/50 (12.0)	-	-

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LLD, lower limit of detection; MAF, mutant allele fraction; NE, not evaluable; OR, odds ratio; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Gotlib et al. (2023).³¹

2.7.4 Health-related quality of life in PIONEER randomised phase

2.7.4.1 MC-QoL at 24 weeks: Avapritinib vs placebo

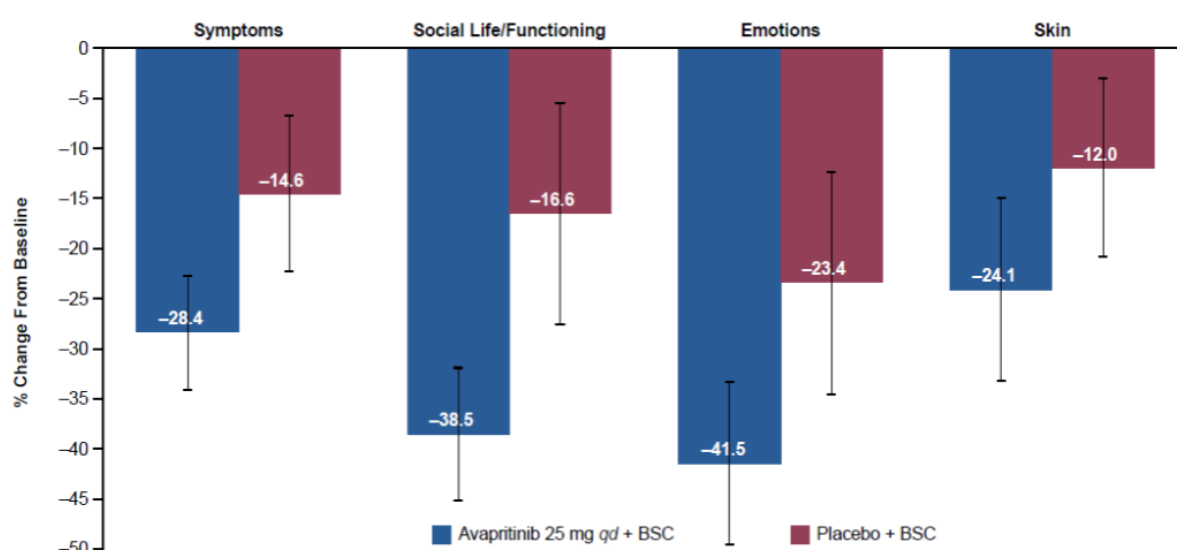
The MC-QoL is a 27-item instrument specifically designed for participants with mastocytosis, with higher scores indicating greater impairment (range 0-100).³¹

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At baseline, mean total MC-QoL scores were similar between treatment groups: 57.50 (16.02) for avapritinib and 57.47 (17.20) for placebo. By Week 24, avapritinib-treated participants showed greater improvements across all domains compared with placebo (Figure 16). The largest mean percent reductions with avapritinib were observed in the emotions score (-41.47%) and social life/functioning score (-38.52%).³¹

A post-hoc sensitivity analysis excluding French translations (due to mistranslation issues) was consistent with the overall analysis.⁵⁴

Figure 16. Change in MC-QoL from baseline at Week 24 (PIONEER Part 2 ITT Population)



Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.
Abbreviations: BSC, best supportive care; ITT, intent-to-treat; MC-QoL, Mastocytosis Quality of Life Questionnaire; SD, standard deviation; SDT, symptom-directed therapy.
Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Gotlib et al. (2023).³¹

2.7.4.2 PGIS and PGIC at 24 weeks: Avapritinib vs placebo

The PGIS measures disease severity on a 0-4 scale, with decreases indicating improvement. The PGIC measures overall improvement on a 1-7 scale, with higher scores indicating greater improvement (Table 19).⁵⁴

At baseline, mean (SD) PGIS scores were identical between groups: [REDACTED] for avapritinib and [REDACTED] for placebo. By Week 24, avapritinib-treated participants showed a greater reduction in PGIS (mean change: [REDACTED] for placebo).

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For PGIC (measured only post-baseline), avapritinib-treated participants reported greater improvement compared with placebo at all timepoints. At Week 24, the mean (SD) PGIC score was [REDACTED] for avapritinib versus [REDACTED] for placebo, indicating "moderate improvement" versus "minimal improvement," respectively.⁵⁴

Table 19. Change in PGIS and PGIC from baseline at Week 24 (PIONEER Part 2 ITT Population)

Measure	Avapritinib 25mg	Placebo
PGIS		
N	[REDACTED]	[REDACTED]
Baseline mean (SD)	[REDACTED]	[REDACTED]
Change from baseline mean (SD)	[REDACTED]	[REDACTED]
PGIC		
N	[REDACTED]	[REDACTED]
Score at Week 24 (SD)	[REDACTED]	[REDACTED]

Abbreviations: : ITT, intent-to-treat; PGIC; Patient Global Impression of Change; PGIS, Patient Global Impression of Symptom Severity; SD, standard deviation

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴

2.7.4.3 SF-12 at 24 weeks: Avapritinib vs placebo

The SF-12 measures HRQoL, yielding Physical Component Summary (PCS) and MCS scores, with increases indicating improvement.⁵⁴

At baseline, mean scores were comparable between groups: PCS scores of 33.83 (10.79) for avapritinib and 34.07 (10.70) for placebo; MCS scores of 40.60 (10.51) for avapritinib and 40.99 (10.67) for placebo.⁸³

By Week 24, avapritinib-treated participants showed greater improvements in both components compared with placebo (Table 20). The mean percent increase in the PCS score was 19.95% with avapritinib versus 12.14% with placebo, while the MCS score increased by 12.34% with avapritinib versus 6.28% with placebo.^{31,54}

Table 20. Change in SF-12 from baseline at Week 24 (PIONEER Part 2 ITT Population)

SF-12 component	Avapritinib 25 mg N=120	Placebo N=59
Physical component summary		
Baseline: mean (SD)	33.83 (10.79)	34.07 (10.70)
Mean (SD) change	5.60 (8.43)	3.08 (7.01)
Mean (SD) percent change	19.95 (30.90)	12.14 (26.59)
Mental component summary		
Baseline: Mean (SD)	40.60 (10.51)	40.99 (10.67)
Mean (SD) change	3.92 (9.27)	1.62 (9.03)
Mean (SD) percent change	12.34 (26.57)	6.28 (26.93)

Abbreviations: ITT, intent-to-treat; SD, standard deviation; SF-12, 12-item Short Form Health Survey.
Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Akin et al. (2023).⁸³

2.7.4.4 EQ-5D-5L (VAS) at 24 weeks: Avapritinib vs placebo

The EQ-5D-5L (VAS) measures self-rated health status on a 0-100 scale, with increases in score indicating improvement.^{83,84}

At baseline, mean (SD) VAS scores were similar between groups: 57.2 (17.61) for avapritinib and 55.9 (17.85) for placebo. By Week 24, avapritinib-treated participants showed a greater improvement compared with placebo (Table 21). The mean increase in VAS score was 6.6 points (18.5% improvement) with avapritinib versus only 0.1 points (4.5% improvement) with placebo.^{54,83}

Table 21. Change in EQ-5D-5L (VAS) from baseline at Week 24 (PIONEER Part 2 ITT Population)

Measure	Avapritinib 25mg	Placebo
EQ-5D-5L (VAS)		
N	121	59
Baseline mean (SD)	57.2 (17.61)	55.9 (17.85)
Change from baseline mean (SD)	6.6 (18.84)	0.1 (13.58)
Percent change from baseline mean (SD)	18.5% (48.83%)	4.5% (32.29%)

Abbreviations: EQ-5D-5L, EuroQoL 5-Dimension 5-Level questionnaire; ITT, intent-to-treat; SD, standard deviation; VAS, Visual Analogue Scale
Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Akin et al. (2023).⁸³

2.7.5 Anaphylaxis frequency at Week 24: Avapritinib vs placebo

Exploratory analyses of the change in number of episodes of anaphylaxis events were conducted in a subset of 13 PIONEER participants who experienced anaphylactic reactions requiring epinephrine (10 avapritinib, 3 placebo).⁸⁵ Amongst

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avapritinib-treated patients, 8 of 10 who experienced anaphylaxis during the 12-week screening period had no anaphylactic events during the 24-week treatment period. In contrast, all 3 placebo patients experienced anaphylaxis only during the treatment period, with no events during screening. The event rate during Part 2 ranged from 0.00 to 0.67 events per month in the avapritinib group compared to 0.17 to 0.67 events per month in the placebo group.⁸⁵

2.7.6 Symptom-directed therapy medication usage at 24 weeks: Avapritinib vs placebo

At Week 24, avapritinib demonstrated a reduction in SDT medication usage compared to placebo.⁸⁶ Of patients treated with avapritinib, 21% (30/141) decreased SDT usage after 24 weeks versus 13% (9/71) of patients treated with placebo. Of patients treated with avapritinib, 3% (4/141) were able to completely discontinue SDT (including 1 patient receiving 5 SDT before treatment) versus 0% patients treated with placebo. Patients treated with avapritinib were more likely to decrease or discontinue SDT to manage ISM symptoms compared to placebo.⁸⁶

2.7.7 Long-term avapritinib efficacy in PIONEER open-label extension phase

2.7.7.1 Change in overall symptom score (ISM-SAF TSS) from baseline at 1, 2 and 3 years

In the ITT population, avapritinib treatment demonstrated substantial and sustained reductions in ISM-related symptom severity throughout 3 years of treatment. Mean (SD) reductions from baseline of 18 points (19.1) in TSS were observed at 1 year of treatment with avapritinib, with sustained reductions maintained through 2 years [17.8 (21.9) points] and 3 years [19.4 (20.0) points] of treatment (Table 22). These reductions were consistent regardless of participants' starting dose of avapritinib.⁸⁰

The PP population showed comparable results to the ITT population, with mean (SD) reductions from baseline of [REDACTED] points in TSS observed at 1 year of treatment with avapritinib, with further sustained reductions observed at 2 years [REDACTED] points] and 3 years [REDACTED] points] of treatment (Table 23).

In both Safety and PP populations, in participants who maintained a 25-mg dose of avapritinib as of the time of the data cut, comparable reductions in TSS were

demonstrated at 1, 2 and 3 years of treatment, with similar proportions of participants exhibiting meaningful symptom improvements. Additionally, for participants who underwent dose escalation to 50 mg, further reductions in TSS were observed from the time of escalation, with sustained improvements demonstrated at 6 months and 1 year after dose escalation, meeting clinical criteria for dose increase (see Appendix M).⁸⁰

Table 22. Change in ISM-SAF TSS from baseline up to 3 years avapritinib (PIONEER Part 3 ITT population)

Parameter	Avapritinib 25-mg starting dose (N=226)	Avapritinib all starting doses (N=████)
Baseline		
N	224	████
TSS, mean (SD)	48.1 (19.5)	██████████
~ 1 year from baseline (C13 D1)		
N	195	████
TSS, mean (SD)	29.6 (20.5)	██████████
TSS change from baseline, mean (SD)	-17.7 (19.3)	██████████
Percent TSS change from baseline, mean (SD)	-35.6 (39.0)	██████████
~ 2 years from baseline (C25D1)		
N	165	████
TSS, mean (SD)	29.6 (22.2)	██████████
TSS change from baseline, mean (SD)	-17.5 (22.2)	██████████
Percent TSS change from baseline, mean (SD)	-32.3 (50.1)	██████████
~ 3 years from baseline (C40D1)		
N	129	████
TSS, mean (SD)	27.9 (19.7)	██████████
TSS change from baseline, mean (SD)	-19.4 (20.1)	██████████
Percent TSS change from baseline, mean (SD)	-37.8 (40.1)	██████████

Abbreviations: CxDx, Cycle x, Day x; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; SD, standard deviation; TSS, total symptom score.

Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.

Source: Blueprint Medicines Corporation Clinical Study Report (2025).⁸⁰

Table 23. Change in ISM-SAF TSS from baseline up to 3 years avapritinib (PIONEER Part 3 PP population)

Parameter	Avapritinib 25-mg starting dose (N=████)	Avapritinib all starting doses (N=████)
Baseline		
N	████	████
TSS, mean (SD)	██████████	██████████
~ 1 year from baseline (C13 D1)		
N	████	████
TSS, mean (SD)	██████████	██████████
TSS change from baseline, mean (SD)	██████████	██████████
Percent TSS change from baseline, mean (SD)	██████████	██████████
~ 2 years from baseline (C25D1)		
N	████	████
TSS, mean (SD)	██████████	██████████
TSS change from baseline, mean (SD)	██████████	██████████
Percent TSS change from baseline, mean (SD)	██████████	██████████
~ 3 years from baseline (C40D1)		
N	████	████
TSS, mean (SD)	██████████	██████████
TSS change from baseline, mean (SD)	██████████	██████████
Percent TSS change from baseline, mean (SD)	██████████	██████████

Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Abbreviations: CxDx, Cycle x, Day x; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PP, per-protocol; SD, standard deviation; TSS, total symptom score. Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.7.2 Percentage of patients with ISM achieving 30% and 50% reductions in TSS at 1, 2 and 3 years avapritinib treatment

Long-term treatment with avapritinib demonstrated sustained clinically meaningful response rates, with consistent proportions of participants achieving both moderate ($\geq 30\%$) and substantial ($\geq 50\%$) reductions in symptom burden at 1 year from baseline across different analysis populations (Table 24).⁸⁰

In the ITT population, █████ of participants achieved a $\geq 30\%$ reduction in TSS by 1 year from baseline, while █████ of participants achieved a $\geq 50\%$ reduction in TSS.

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These response rates were consistent regardless of participants' starting dose of avapritinib.⁸⁰

The PP population showed comparable response rates to the ITT population, where [REDACTED] of participants had a $\geq 30\%$ reduction in TSS and [REDACTED] of participants had a $\geq 50\%$ reduction in TSS at 1 year from baseline.⁸⁰

When considering participants in both the ITT population and the PP population who maintained a 25-mg dose of avapritinib, similar proportions of participants exhibited $\geq 30\%$ and $\geq 50\%$ reductions in TSS after 1 year of treatment as the overall populations. For participants who underwent dose escalation to 50 mg, response rates were also observed from the time of escalation, demonstrating additional benefit for patients meeting clinical criteria for dose increase (see Appendix M).⁸⁰

Table 24. Proportion of participants with $\geq 50\%$ and $\geq 30\%$ reduction in ISM-SAF TSS up to 3 years avapritinib (PIONEER Part 3)

Population	Avapritinib 25-mg starting dose	Avapritinib all starting doses
ITT population		
Total N	██████████	██████████
Proportion with $\geq 30\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	██████████	██████████
Proportion with $\geq 50\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	██████████	██████████
Per-Protocol Population		
Total N	██████████	██████████
Proportion with $\geq 30\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	██████████	██████████
Proportion with $\geq 50\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	██████████	██████████

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The reported patient numbers were used in the calculation of mean TSS score.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; TSS, total symptom score; PP, per-protocol.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.7.3 Objective measures of mast cell burden at 1, 2 and 3 years avapritinib treatment

Reductions in serum tryptase levels relative to baseline were evident with long-term avapritinib treatment, with median percent reductions from baseline of ██████████ observed in the ITT population at 1 year of treatment, which were maintained as of 2 years (██████████) and 3 years (██████████) of treatment (Table 25). These findings were observed irrespective of participants' starting dose of avapritinib. While median concentrations of serum tryptase at baseline were > 20 ng/mL, a level that satisfies

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one of the minor criteria for a diagnosis of SM, median concentrations at 1, 2 and 3 years of post-baseline follow-up were below this threshold, irrespective of participants' starting dose of avapritinib.⁸⁰

In the PP population, median percent reductions from baseline of [REDACTED] were observed at 1 year of treatment, maintained at 2 years ([REDACTED]) and 3 years ([REDACTED]) of treatment, with these findings observed irrespective of participants' starting dose of avapritinib (Table 26).⁸⁰

Comparable reductions in serum tryptase at 1, 2 and 3 years of treatment were noted in participants across both Safety and PP populations who maintained a 25-mg dose of avapritinib as of the time of the data cut. For participants who underwent dose escalation to 50 mg, further reductions in serum tryptase were observed from the time of escalation, demonstrating additional benefit for patients meeting clinical criteria for dose increase (see Appendix M).⁸⁰

Table 25. Change in serum tryptase from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT Population		PP Population	
	25-mg starting dose	All starting doses	25-mg starting dose	All starting doses
Baseline				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Concentration, median, ng/mL (range)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~ 1 year from baseline (C13 D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Concentration, median, ng/mL (range)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in concentration from baseline, median, ng/mL (range)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent change in concentration from baseline, median (range)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~ 2 years from baseline (C25D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Concentration, median, ng/mL (range)				
Change in concentration from baseline, median, ng/mL (range)				
Percent change in concentration from baseline, median (range)				
~ 3 years from baseline (C40D1)				
N				
Concentration, median, ng/mL (range)				
Change in concentration from baseline, median, ng/mL (range)				
Percent change in concentration from baseline, median (range)				

Abbreviations: CxDx, Cycle x, Day x; ITT, intention-to-treat; PP, per-protocol
Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

Table 26. Change in *KIT* D816V VAF from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25-mg starting dose	All starting doses	25-mg starting dose	All starting doses
Baseline				
N				
<i>KIT</i> D816V VAF, median (range)				
~ 1 year from baseline (C13 D1)				
N				
<i>KIT</i> D816V VAF, median (range)				
Change in <i>KIT</i> D816V VAF from baseline,				

Parameter	ITT population		PP population	
	25-mg starting dose	All starting doses	25-mg starting dose	All starting doses
median (range)				
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)				
~ 2 years from baseline (C25D1)				
N				
<i>KIT</i> D816V VAF, median (range)				
Change in <i>KIT</i> D816V VAF from baseline, median (range)				
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)				
~ 3 years from baseline (C40D1)				
N				
<i>KIT</i> D816V VAF, median (range)				
Change in <i>KIT</i> D816V VAF from baseline, median (range)				
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)				

Abbreviations: CxDx, Cycle x, Day x; ITT, intention-to-treat; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PP, per-protocol; VAF, variant allele frequency.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.7.4 Health-related quality of life

2.7.7.4.1 MC-QoL at 1, 2 and 3 years avapritinib treatment

In the ITT population, reductions in mean MC-QoL total score of [REDACTED] points were observed at 1 year of avapritinib treatment, which were maintained after 2 years ([REDACTED] points) and 3 years ([REDACTED] points) of treatment.⁸⁰

In the PP population, reductions in mean MC-QoL total score of [REDACTED] points was observed at 1 year of avapritinib treatment, which were maintained as of 2 years ([REDACTED]) and 3 years ([REDACTED]) of treatment (Table 27).⁸⁰

Participants who maintained a 25-mg dose of avapritinib across both Safety and PP populations showed comparable reductions in mean MC-QoL total score from baseline to 1, 2 and 3 years of post-baseline follow-up as the overall populations.⁸⁰

Table 27. Change in MC-QoL total score from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25-mg starting dose (N=226)	All starting doses (N=246)	25-mg starting dose (N=203)	All starting doses (N=220)
Baseline				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
MC-QoL total score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~ 1 year from baseline (C13 D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
MC-QoL total score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in MC-QoL total score from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent change in MC-QoL total score from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~ 2 years from baseline (C25D1)				

N	████	████	████	████
MC-QoL score, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████
Change in MC-QoL total score from baseline, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████
Percent change in MC-QoL total score from baseline, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████
~ 3 years from baseline (C40D1)				
N	████	████	████	████
MC-QoL score, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████
Change in MC-QoL total score from baseline, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████
Percent change in MC-QoL total score from baseline, mean (SD)	████████████████████	████████████████████	████████████████████	████████████████████

Abbreviations: CxDx, Cycle x, Day x; MC-QoL, ITT, intention-to-treat; Mastocytosis Quality of Life; PP, per-protocol; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.7.4.2 EQ-5D-5L at 1, 2 and 3 years

Increases in mean EQ-5D-5L scores from baseline to 1year (████), 2 years (████) and 3 years (████) of avapritinib treatment in the ITT population were observed, indicating sustained improvements in HRQoL. Improvements in mean EQ-5D-5L scores were consistent in the PP population, with increases of █████ at 1 year, █████ at 2 years, and █████ at 3 (Table 28).⁸⁰

Improvements also remained consistent, regardless of participants' starting dose of avapritinib and whether a 25-mg dose of avapritinib had been maintained as of the time of the data cut across both Safety and PP populations.⁸⁰

Table 28. Change in EQ-5D-5L scores from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25-mg starting dose (N=████)	All starting doses (N=████)	25-mg starting dose (N=████)	All starting doses (N=████)
Baseline				
N	████	████	████	████
EQ-5D-5L score, mean (SD)	██████████	██████████	██████████	██████████
~ 1 year from baseline (C13 D1)				
N	████	████	████	████
EQ-5D-5L score, mean (SD)	██████████	██████████	██████████	██████████
Change in EQ-5D-5L score from baseline, mean (SD)	██████████	██████████	██████████	██████████
Percent change in EQ-5D-5L score from baseline, mean (SD)	██████████	██████████	██████████	██████████
~ 2 years from baseline (C25D1)				
N	████	████	████	████
EQ-5D-5L score, mean (SD)	██████████	██████████	██████████	██████████
Change in EQ-5D-5L score from baseline, mean (SD)	██████████	██████████	██████████	██████████
Percent change in EQ-5D-5L score from baseline, mean (SD)	██████████	██████████	██████████	██████████
~ 3 years from baseline (C40D1)				

N				
EQ-5D-5L score, mean (SD)				
Change in EQ-5D-5L score from baseline, mean (SD)				
Percent change in EQ-5D-5L score from baseline, mean (SD)				

Abbreviations: CxDx, Cycle x, Day x; EQ-5D-5L, EuroQoL 5-Dimension 5-Level questionnaire; ITT, intention-to-treat; PP, per-protocol; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.8 SF-12 at 1, 2 and 3 years

Participants in both the ITT and PP populations demonstrated sustained improvements in HRQoL as measured by the SF-12 PCS and MCS throughout the 3 year treatment period (⁸⁰

Table 29).^{80,87}

In the ITT population, mean SF-12 PCS scores increased from baseline by [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years for participants receiving all starting doses. Corresponding improvements in mean SF-12 MCS scores were [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years.⁸⁰

The PP population demonstrated comparable improvements in both PCS and MCS. Mean SF-12 PCS scores increased from baseline by [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years for participants receiving all starting doses. Mean SF-12 MCS scores showed improvements of [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years.⁸⁰

These improvements in SF-12 scores were consistent regardless of participants' starting dose of avapritinib and were maintained across both analysis populations.⁸⁰

Table 29. Change in SF-12 physical and mental component scores from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25-mg starting dose (N=)	All starting doses (N=)	25-mg starting dose (N=)	All starting doses (N=)
Physical component summary				
Baseline				
N				
SF-12 PCS, mean (SD)				
~1 year from baseline (C13D1)				
N				
SF-12 PCS, mean (SD)				
Change in SF-12 PCS from baseline, mean (SD)				
Percent change in SF-12 PCS from baseline, mean (SD)				
~2 years from baseline (C25D1)				
N				
SF-12 PCS, mean (SD)				
Change in SF-12 PCS from baseline, mean (SD)				
Percent change in SF-12 PCS from baseline, mean (SD)				
~3 years from baseline (C40D1)				
N				
SF-12 PCS, mean (SD)				
Change in SF-12 PCS from				

baseline, mean (SD)				
Percent change in SF-12 PCS from baseline, mean (SD)				
Mental component summary				
Baseline				
N				
SF-12 MCS, mean (SD)				
~1 year from baseline (C13D1)				
N				
SF-12 MCS, mean (SD)				
Change in SF-12 MCS from baseline, mean (SD)				
Percent change in SF-12 MCS from baseline, mean (SD)				
~2 years from baseline (C25D1)				
N				
SF-12 MCS, mean (SD)				
Change in SF-12 MCS from baseline, mean (SD)				
Percent change in SF-12 MCS from baseline, mean (SD)				
~3 years from baseline (C40D1)				
N				

SF-12 MCS, mean (SD)				
Change in SF-12 MCS from baseline, mean (SD)				
Percent change in SF-12 MCS from baseline, mean (SD)				

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.

Abbreviations: C, Cycle; D, Day; ITT, intention-to-treat; MCS, mental component summary score; PCS, physical component summary score; PP, per-protocol; SD, standard deviation; SF-12, 12-Item Short Form Health Survey.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.9 PGIS and PGIC at 1, 2 and 3 years

In the ITT population, consistent decreases in mean PGIS score were observed from baseline through 3 years of avapritinib treatment, suggesting sustained reductions in symptom severity.^{80,87} For participants receiving all starting doses, mean PGIS scores decreased from baseline by [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years. The PP population demonstrated comparable reductions in PGIS scores, with mean decreases from baseline of [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years for participants receiving all starting doses.⁸⁰ Aligned with PGIS findings, participants in both the ITT and PP populations reported meaningful improvements in their symptom severity whilst on treatment.

In the ITT population, mean PGIC scores of approximately [REDACTED] points were observed at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years post-baseline for participants receiving all starting doses. The PP population showed similar PGIC scores, with mean values of [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years for participants receiving all starting doses (Table 30).⁸⁰

These reductions in PGIS and PGIC were consistent regardless of participants' starting dose of avapritinib and were maintained across both analysis populations throughout the 3-year treatment period.⁸⁰

Table 30. PGIS summary and change from baseline (time of avapritinib initiation) in PGIS up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25-mg starting dose (N=)	All starting doses (N=)	25-mg starting dose (N=)	All starting doses (N=)
PGIS				
Baseline				
N				
PGIS score, mean (SD)				
~1 year from baseline (C13D1)				
N				
PGIS score, mean (SD)				
Change in PGIS score from baseline, mean (SD)				
~2 years from baseline (C25D1)				
N				
PGIS score, mean (SD)				
Change in PGIS score from baseline, mean (SD)				
~3 years from baseline (C40D1)				
N				
PGIS score, mean (SD)				
Change in PGIS score from baseline, mean (SD)				
PGIC (7-point scale)				
~1 year from baseline (C13D1)				
N				
PGIC score, mean (SD)				
~2 years from baseline (C25D1)				
N				
PGIC score, mean (SD)				
~3 years from baseline (C40D1)				
N				
PGIC score, mean (SD)				

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The PGIS scale ranges from 0 (none) to 4 (very severe). The PGIC scale ranges from 1 (very much worse) to 7 (very much better), with a score of 4 indicating no change and 5 indicating moderately better.

Abbreviations: C, Cycle; D, Day; ITT, intention-to-treat; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Symptom Severity; PP, per-protocol; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.10 Symptom-directed therapy medication usage alongside avapritinib at 33 months

At baseline, 99.1% of participants in the PP population were using at least one concomitant SDT therapy to manage ISM symptoms, including IgE antibodies, corticosteroids, cromolyn sodium, histamine H1 and H2 antihistamines, leukotriene inhibitors and proton-pump inhibitors. Notably, 31.8% of participants were receiving ≥ 4 SDT therapies at baseline. Long-term avapritinib treatment markedly reduced participants' use of supplementary SDT therapies.⁸⁰

At 33 months (in participants who reached C37D1 or discontinued before C37D1), 53.9% of participants (all starting doses) experienced an improvement in SDT use (change in dose or schedule) in at least one class of therapy. Among participants with improved SDT use, 32.3% improved in one class, 14.7% in two classes, 6.5% in three classes and 0.5% in four classes. The most commonly improved SDT therapy classes were H1 antihistamines (12.9%), H2 antihistamines (11.5%) and cromolyn sodium (2.8%).⁸⁰

Table 31. Change from baseline (time of avapritinib initiation) in SDT use in the PP population at 33 months avapritinib (PIONEER Part 3)

Parameter	25-mg starting dose (N=200)	All starting doses (N=████)
Baseline		
Participants with SDT use		
At least one therapy, n (%)	198 (99.0)	██████████
Anti-IgE antibody, n (%)	24 (12.0)	██████████
Corticosteroids, n (%)	24 (12.0)	██████████
Cromolyn sodium, n (%)	66 (33.0)	██████████
H1 antihistamines, n (%)	196 (98.0)	██████████
H2 antihistamines, n (%)	136 (68.0)	██████████
Leukotriene inhibitors, n (%)	82 (41.0)	██████████
Proton-pump inhibitors, n (%)	40 (20.0)	██████████
Other, n (%)	40 (20.0)	██████████
Number of classes of SDT used		
One class, n (%)	16 (8.0)	██████████
Two classes, n (%)	57 (28.5)	██████████
Three classes, n (%)	62 (31.0)	██████████
≥Four classes, n (%)	63 (31.5)	██████████
C37D1*		
Number of classes improved		
At least one class, n (%)	107 (53.5)	██████████
One class, n (%)	64 (32.0)	██████████
H1 antihistamines, n (%)	28 (14.0)	██████████
H2 antihistamines, n (%)	21 (10.5)	██████████
Cromolyn sodium, n (%)	5 (2.5)	██████████
Anti-IgE antibody, n (%)	5 (2.5)	██████████
Other individual classes, n (%)	5 (2.5)	██████████
Two classes, n (%)	32 (16.0)	██████████
Three classes, n (%)	10 (5.0)	██████████
Four classes, n (%)	1 (0.5)	██████████

Note:*Includes participants who had reached C37D1 or discontinued before C37D1 as of the February 21, 2025 data cut. Participants who initiated avapritinib at 50 mg or 100 mg in Part 1 continued treatment at 25 mg daily at the start of Part 3. Abbreviations: C, Cycle; D, Day; H1, histamine H1 receptor; H2, histamine H2 receptor; IgE, immunoglobulin E; PP, per-protocol; SDT, symptom-directed therapy.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.7.11 Bone mineral density after 2 years of avapritinib treatment

Exploratory bone health assessments revealed high prevalence of bone-related comorbidities, with osteopenia in 48 patients (19%) and osteoporosis in 56 patients

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(22%) amongst 251 enrolled participants.⁸⁸ In a single-site cohort of 13 patients with serial dual-energy X-ray absorptiometry measurements, mean bone mineral density increases of $4.79 \pm 4.78\%$ at the lumbar spine and $3.59 \pm 5.58\%$ at the femoral neck were observed after 2 years of avapritinib treatment. At baseline, 8 patients had osteopenia (T-score between -2.5 and -1) and 2 had osteoporosis (T-score ≤ -2.5).⁸⁸

2.8 Subgroup analysis

In the PIONEER study, subgroup analyses were performed for the primary and key secondary efficacy endpoints, as well as for adverse events based on age, sex, country baseline ISM status, ECOG performance scores, baseline serum tryptase level and prior TKI therapy. The subgroup analyses for efficacy generally demonstrated that avapritinib provided benefits across most subgroups in terms of ISM-SAF TSS reduction and objective measures of mast cell burden at 24 weeks.⁵⁴

Minor numerically differential treatment effects (not statistically significant) were observed in ISM-SAF TSS reduction, by gender, with the mean difference in ISM-SAF TSS between avapritinib and placebo groups being [REDACTED] points in males versus [REDACTED] points in females, though the limited male sample size (n=17 in the placebo group and n=[REDACTED] in the avapritinib group) precludes definitive conclusions.⁵⁴ Baseline serum tryptase levels also influenced treatment response, with patients having < 20 ng/mL showing a difference of 1.58 points compared to -8.63 points in patients with ≥ 20 ng/mL. The subgroup with baseline serum tryptase levels < 20 ng/mL also had small sample size (n=14 in the placebo group and n=27 in the avapritinib group).^{31,54}

On the safety front, avapritinib's AE profile remained consistent across the majority of subgroups, with no new signals identified even with longer treatment duration in Part 3 and overall analyses.^{54,80}

A summary of the results for these subgroups is provided in Appendix C.

2.9 Meta-analysis

No meta-analysis was conducted by Blueprint Medicines Corporation as part of this NICE submission.

2.10 Indirect and mixed treatment comparisons

No indirect treatment comparisons were conducted by Blueprint Medicines Corporation as part of this NICE submission.

2.11 Adverse reactions

2.11.1 Part 1 safety results

In Part 1 of the PIONEER trial, the mean duration of treatment was similar across groups, ranging from [REDACTED] weeks. The incidence of AEs was similar across treatment groups (Table 32). There [REDACTED] in the 50 mg avapritinib group due to an AE of delirium. AEs leading to dose modifications occurred in [REDACTED] of placebo participants and in [REDACTED] of the 25 mg, 50 mg and 100 mg avapritinib-treated participants respectively.

The most common AEs (>15%) in either group (placebo; avapritinib all doses) were

[REDACTED]

[REDACTED] were noted only in avapritinib-treated participants.⁵⁴

No events of intracranial bleeding (ICB) were reported. Among cognitive effect events, AEs of cognitive disorder and memory impairment were reported in one patient each in the 25 mg and 100 mg groups respectively, and a serious adverse event (SAE) of delirium was reported in one patient in the 50 mg group. Most of these events were non-serious and Grade 1 or 2. The SAE of delirium was Grade 3 and led to study drug discontinuation. No cognitive effect events were reported in the placebo group.

Overall, avapritinib was well-tolerated across all doses. The 25 mg dose was very well-tolerated, with a similar safety profile compared to placebo. There were no Grade ≥ 3 AEs, no SAEs, no dose modifications and no discontinuations at the 25 mg dose level.

No deaths or clinically significant trends for clinical laboratory tests, vital signs, ECGs and physical examination were reported.⁵⁴

Table 32. Summary of adverse events (PIONEER Part 1 ITT population)

Parameter	Placebo (N=9) n (%)	Avapritinib 25 mg (N=10) n (%)	Avapritinib 50 mg (N=10) n (%)	Avapritinib 100 mg (N=10) n (%)
Any AEs	██████████	██████████	██████████	██████████
Related AEs	██████████	██████████	██████████	██████████
Serious AEs	██████████	██	██████████	██
Grade 3 or higher AEs	██████████	██	██████████	██████████
AEs leading to dose modifications	██████████	██	██████████	██████████
AEs leading to study drug discontinuation	██	██	██████████	██
Deaths	██	██	██	██

Abbreviations: AE, adverse event; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022).⁵⁴

2.11.2 Part 2 safety results

In Part 2, 141 participants were exposed to 25 mg avapritinib and 71 participants to placebo. The mean (SD) treatment duration was 5.46 (0.726) months in the 25 mg avapritinib group and 5.43 (0.806) months in the placebo group.³¹ The median relative dose intensity in the 25 mg avapritinib group was 100% (range: 83% to 101%).⁵⁴

The safety profile of 25 mg avapritinib QD was similar to that of placebo (Table 33). Overall, 90.8% of participants in the 25 mg avapritinib group and 93.0% in the placebo group experienced at least one AE. Drug-related AEs occurred in 54.6% of avapritinib participants versus 45.1% of placebo participants. The proportion of participants with SAEs was lower with avapritinib (5.0%) than placebo (11.3%), with no drug-related SAEs in either group.^{31,54}

The most common AEs ($\geq 10\%$) included headache, nausea, COVID-19, dizziness and diarrhoea. Face oedema was the only AE with $>5\%$ higher incidence in the avapritinib group (7.1% vs 1.4%).³¹ Oedema events were more frequent with avapritinib (██████████) than placebo (██████████), with most being Grade 1 or 2 in severity (majority Grade 1) and no AEs were Grade ≥ 3 .⁵⁴

Cognitive effect events were infrequent and reported in a slightly lower proportion of avapritinib participants (2.8%) than placebo participants (4.2%).³¹ The most common was memory impairment (██████████).⁵⁴

For laboratory evaluations, there were no clinically relevant differences between groups in haematology parameters. There were no deaths during Part 2 of the study.⁵⁴

Table 33. Overview of safety results (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg (N=141) n (%)	Placebo (N=71) n (%)
General safety summary		
Participants with at least 1 AE	128 (90.8)	66 (93.0)
AE-related to study drug	77 (54.6)	32 (45.1)
SAE	7 (5.0)	8 (11.3)
SAE related to study drug	0	0
Grade 1 AE	48 (34.0)	15 (21.1)
Grade 2 AE	50 (35.5)	36 (50.7)
Grade ≥ 3 AE	30 (21.3)	15 (21.1)
Grade ≥ 3 AE-related to study drug	3 (2.1)	2 (2.8)
AE leading to interruption of study drug	12 (8.5)	9 (12.7)
AE leading to dose reduction of study drug	2 (1.4)	1 (1.4)
AE leading to permanent discontinuation	3 (2.1)	1 (1.4)
Death	0	0
Common AEs (≥ 10% in either group)		
Headache	27 (19.1)	14 (19.7)
Nausea	18 (12.8)	12 (16.9)
COVID-19	17 (12.1)	8 (11.3)
Dizziness	16 (11.3)	6 (8.5)
Diarrhoea	15 (10.6)	8 (11.3)
Oedema events		
Participants with at least 1 AE of oedema	36 (25.5)	8 (11.3)
Oedema peripheral	12 (8.5)	3 (4.2)
Face oedema	10 (7.1)	1 (1.4)
Periorbital oedema	9 (6.4)	2 (2.8)
Cognitive effect events		
Participants with at least 1 AE of cognitive effect	4 (2.8)	3 (4.2)
Memory impairment	2 (1.4)	1 (1.4)
Amnesia	1 (0.7)	0
Mood altered	1 (0.7)	0
Mental impairment	0	1 (1.4)

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Parameter	Avapritinib 25 mg (N=141) n (%)	Placebo (N=71) n (%)
Mental status changes	0	1 (1.4)

Abbreviations: AE, adverse event; COVID-19, Coronavirus disease 2019; ITT, intention-to-treat; SAE, serious adverse event.

Sources: Blueprint Medicines Corporation PIONEER Clinical Study Report (2022)⁵⁴; Gotlib et al. 2023³¹

2.11.3 PIONEER open-label extension safety results

According to the latest PIONEER OLE (Part 3) data cut, which included participants who completed Parts 1 or 2 and rolled over into the open-label extension, the mean duration of treatment in the ITT population was [REDACTED] months for participants who initiated avapritinib at 25 mg starting dose and [REDACTED] months for participants who initiated avapritinib at all starting doses. The median duration of treatment was 40.0 months (range: 0.7, 67.2) and 40.1 months (range: 0.2, 67.2), respectively. The majority of participants had ≥6 months on treatment [REDACTED] respectively), ≥12 months on treatment ([REDACTED] % respectively), ≥24 months on treatment ([REDACTED] % respectively) and ≥36 months on treatment ([REDACTED] respectively).⁸⁰

A summary of AEs from PIONEER Part 3, as of the latest DCO, is presented in Table 34.⁸⁰ AE profiles were comparable between participants who initiated avapritinib at 25 mg (99.1%) and participants who initiated avapritinib at any dose (98.8%) and between the entire safety (ITT) population and participants in the ITT population who maintained a 25 mg dose as of the time of the data cut (see Table 35 for AEs in ≥10% participants and Table 36 for SAEs in ≥2% of participants). Further information on the safety profile of the OLE phase of the PIONEER trial is included in Appendix D (Adverse reactions). No new safety concerns were observed in patients who dose-escalated to 50 mg (see Appendix M).⁸⁰

Table 34. Summary of AEs in PIONEER safety population at DCO

Participants with at least one event, n (%)	25-mg starting dose (N=226)	All starting doses (N=246)
Any AE		
AE-related to study drug		
SAE		
SAE related to study drug		
Grade ≥3 AE		
Grade ≥3 AE-related to study drug		
AE leading to interruption of study drug		
AE-related to study drug leading to interruption of study drug		
AE leading to reduction of study drug		
AE-related to study drug leading to reduction of study drug		
AE leading to permanent discontinuation of study drug		
AE-related to study drug leading to permanent discontinuation of study drug		
AE leading to death		

Abbreviations: AE, adverse event; DCO, data cut-off; ITT, intention-to-treat; SAE, serious adverse event.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

In terms of AEs reported as of the DCO, avapritinib demonstrated a consistent safety profile with most frequent AEs (≥10% of safety population) including

across the analysis populations (Table 35).

Notably, no new safety concerns were observed as per the latest DCO compared to previously reported timepoints.

Table 35: AEs that occurred in ≥10% of the PIONEER safety population (Avapritinib, all starting doses) at DCO

Patients with at least one event by preferred term, n (%)	Avapritinib, 25-mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25-mg dose maintained (N=175)	Avapritinib, 25-mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
■	159 (98.8)	172 (98.3)	224 (99.1)	243 (98.8)
■	75 (46.6)	79 (45.1)	115 (50.9)	123 (50.0)
■	34 (21.1)	40 (22.9)	54 (23.9)	63 (25.6)
■	38 (23.6)	43 (24.6)	54 (23.9)	60 (24.4)
■	31 (19.3)	40 (22.9)	49 (21.7)	60 (24.4)
■	31 (19.3)	36 (20.6)	52 (23.0)	57 (23.2)
■	25 (15.5)	28 (16.0)	43 (19.0)	47 (19.1)
■	24 (14.9)	27 (15.4)	41 (18.1)	46 (18.7)
■	30 (18.6)	34 (19.4)	40 (17.7)	45 (18.3)
■	29 (18.0)	32 (18.3)	35 (15.5)	42 (17.1)
■	22 (13.7)	23 (13.1)	35 (15.5)	37 (15.0)
■	21 (13.0)	21 (12.0)	32 (14.2)	36 (14.6)
■	26 (16.1)	27 (15.4)	34 (15.0)	35 (14.2)
■	15 (9.3)	19 (10.9)	27 (11.9)	34 (13.8)
■	23 (14.3)	25 (14.3)	31 (13.7)	34 (13.8)
■	14 (8.7)	17 (9.7)	30 (13.3)	33 (13.4)
■	18 (11.2)	22 (12.6)	27 (11.9)	32 (13.0)
■	18 (11.2)	22 (12.6)	27 (11.9)	31 (12.6)
■	17 (10.6)	19 (10.9)	27 (11.9)	30 (12.2)
■	15 (9.3)	17 (9.7)	27 (11.9)	29 (11.8)
■	18 (11.2)	20 (11.4)	25 (11.1)	28 (11.4)
■	15 (9.3)	16 (9.1)	24 (10.6)	27 (11.0)
■	17 (10.6)	18 (10.3)	25 (11.1)	26 (10.6)
■	13 (8.1)	13 (7.4)	25 (11.1)	26 (10.6)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; DCO, data cut-off.

Note: Patients who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

Across analysis populations of the PIONEER OLE phase, the number of SAEs was similar for avapritinib 25 mg starting dose group ■ and avapritinib all Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

starting doses ██████████ (Table 36). Though reported as an SAE (ranging ██████████%), anaphylactic reaction is a common clinical manifestation of ISM. As per Table 34, a small number of reported SAEs were deemed to be related to the study drug (avapritinib).

Table 36: SAEs that occurred in ≥2 patients in the PIONEER safety population (Avapritinib, all starting doses) at DCO

Patients with at least one event by preferred term, n (%)	Avapritinib, 25-mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25-mg dose maintained (N=175)	Avapritinib, 25-mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
██████████	30 (18.6)	34 (19.4)	47 (20.8)	54 (22.0)
████████████████████	3 (1.9)	4 (2.3)	7 (3.1)	8 (3.3)
██████████████████	1 (0.6)	2 (1.1)	3 (1.3)	4 (1.6)
██████████████	2 (1.2)	2 (1.1)	3 (1.3)	3 (1.2)
██████████████	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)
████████████████████	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
██████████	0	1 (0.6)	1 (0.4)	2 (0.8)
██████████	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)
██████████████████	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)
████████████████████	0	1 (0.6)	1 (0.4)	2 (0.8)
████████████████████	0	0	2 (0.9)	2 (0.8)
██████████████	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
██████████████████	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
██████████████████	0	0	2 (0.9)	2 (0.8)
██████████████	1 (0.6)	2 (1.1)	1 (0.4)	2 (0.8)

Abbreviations: DCO, data cut-off; SAE, serious adverse event.

Note: Patients who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

2.12 Ongoing studies

- PIONEER OLE: Long-term safety and efficacy (estimated completion 31.01.2028, with early updates to EMA regulatory authority).

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2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Key findings

The pivotal randomised, double-blind PIONEER trial enrolled participants with ISM characteristics reflective of patients seen in clinical practice. In this trial, avapritinib reduced burdensome symptoms and improved disease control whilst being well-tolerated.^{31,54,80,87,89}

2.13.1.1 *Avapritinib recommended dose of 25 mg*

Part 1 established the RP2D through dose escalation comparing 25 mg, 50 mg and 100 mg avapritinib QD doses versus placebo. The 25 mg dose was selected as the RP2D based on comparable efficacy to higher doses with well-tolerated safety profile compared with placebo.⁵⁴ By Week 24, all 3 avapritinib doses achieved similar symptom reductions, with the 25 mg dose demonstrating substantial reductions in objective measures of mast cell burden, including serum tryptase [REDACTED], bone marrow mast cells [REDACTED] and *KIT D816V* allele fraction [REDACTED] compared to placebo.⁵⁴

2.13.1.2 *Avapritinib reduced symptom burden compared to placebo at week 24*

Avapritinib 25 mg QD demonstrated significant and durable improvement in mastocytosis symptoms versus placebo with a 15.6 versus 9.0 point mean reduction from baseline TSS ($p=0.003$) at 24 weeks. Avapritinib-treated participants were significantly more likely than placebo-treated participants to reach the TSS $\geq 30\%$ (45.4% vs 29.6%; $p=0.009$) and TSS $\geq 50\%$ (24.8% vs 9.9%; $p=0.005$) reduction thresholds over time, demonstrating clinically meaningful symptom improvements.⁵⁴

2.13.1.3 *Avapritinib showed disease control compared to placebo at week 24*

Avapritinib showed disease control ($\geq 50\%$ reduction) in participants with ISM compared to placebo, as evidenced by statistically significant improvements in objective disease-related measures. Serum tryptase reduction $\geq 50\%$ was achieved in 53.9% of avapritinib versus 0.0% of placebo participants, *KIT D816V* allele fraction reduction $\geq 50\%$ in 67.8% versus 6.3%, and bone marrow mast cell aggregate reduction $\geq 50\%$ in 52.8% versus 22.8% ($p<0.0001$ for all endpoints).^{31,54}

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2.13.1.4 *Avapritinib improved HRQoL across multiple measures compared to placebo at Week 24*

HRQoL improvements were observed across multiple validated instruments including MC-QoL, PGIC, PGIS, SF-12 and EQ-5D-VAS. Participants on avapritinib reported greater improvement in all HRQoL measures compared with participants on placebo, thus confirming sustained benefit observed in symptom burden. The MC-QoL total score showed particular improvements in the emotions domain (-41.47%) and social life/functioning domain (-38.52%). Regarding concomitant treatment with SDT, twice as many participants were able to have their use of SDT reduced or discontinued compared with participants on placebo (21.3% vs 12.7%). This effect was maintained after 24 weeks of treatment.^{31,54}

2.13.1.5 *Avapritinib provided durable, clinical meaningful improvements in symptoms, disease control and HRQoL compared to placebo up to 3 years*

Long-term efficacy data up to 3 years confirm the durability of the beneficial effect of avapritinib treatment on TSS, measures of mast cell burden (serum tryptase, KIT D816V MAF and bone marrow mast cells) as well as HRQoL. Sustained improvement in TSS was maintained through 3 years of treatment, with mean reductions from baseline of approximately 18-22 points observed consistently across timepoints. Measures of mast cell burden showed durable reductions, with median serum tryptase reductions >50% maintained through 3 years and median concentrations decreasing from above the diagnostic threshold (>20 ng/mL) to below 16 ng/mL. *KIT D816V VAF* demonstrated sustained reductions of [REDACTED] through long-term follow-up.⁸⁰

Long-term data from Part 3 OLE also confirm the durability of the beneficial effect of avapritinib treatment on HRQoL outcomes.⁸⁷ MC-QoL improvements were maintained with approximately 18-point reductions sustained through 3 years of treatment, whilst EQ-5D-5L scores showed consistent improvements across all long-term timepoints.⁸⁰ Additional patient-reported outcomes demonstrated sustained benefits in perceived symptom severity and overall HRQoL with long-term avapritinib treatment. Mean PGIS scores decreased consistently from baseline through 3 years of treatment with avapritinib ([REDACTED]), indicating a

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perceived clinically meaningful reduction in disease symptom severity.⁸⁰ Mean PGIC scores consistently approximated [REDACTED] across the 3-year period, suggesting that people with ISM felt their symptoms were "moderately better" and clinically improved. Improvements in overall HRQoL and disease burden were confirmed by increases in mean SF-12 PCS scores ([REDACTED]) and MCS scores ([REDACTED]) from baseline.⁸⁰

Further, following 2 years of avapritinib treatment (plus SDT), patients demonstrated an increase in bone mineral density (BMD) ranging from 2.21% to 4.79% depending on the measurement site. These magnitudes of bone mineral density improvement equate to a reduced risk of fracture in patients with osteoporosis. While a small sample size, this data alludes to additional benefit conferred by avapritinib, warranting longitudinal, follow-up studies in larger cohorts of patients with ISM.⁸⁸

2.13.1.6 *Avapritinib was well-tolerated in ISM with a safety profile comparable to placebo and consistency across long-term follow-up*

Treatment with avapritinib 25 mg was well-tolerated in ISM participants in the PIONEER trial. The safety profile during Part 2 was comparable to placebo, with 90.8% of avapritinib participants versus 93.0% of placebo participants experiencing at least one adverse event. SAEs were lower with avapritinib (5.0%) than placebo (11.3%), with no drug-related SAEs in either group. The most common adverse events included headache, nausea, dizziness and diarrhoea, with face oedema being the only adverse event with >5% higher incidence in the avapritinib group (7.1% vs 1.4%). Cognitive effect events were infrequent and occurred less frequently with avapritinib (2.8%) than placebo (4.2%). Neurocognitive symptoms are commonly reported in patients with ISM and these results indicate that treatment with avapritinib was not associated with an increased risk of worsening or developing new cognitive effects compared to placebo.^{54,80}

No clinically significant differences were observed in the safety profile for participants treated with avapritinib over an extended period. Long-term safety data throughout the PIONEER study as of the latest data cut showed generally consistent AE profiles with no new safety concerns identified during extended exposure (mean treatment duration 37.1 months over the entire study period). The long-term safety profile up to

3 years remained well-tolerated with low discontinuation rates due to AEs (6.2% over the entire study period).^{54,80,89}

2.13.1.7 *Avapritinib reduced anaphylaxis frequency and symptom-directed therapy usage at Week 24 compared to placebo*

Exploratory analyses revealed potential reductions in anaphylaxis frequency with avapritinib treatment, 75% of patients who had baseline anaphylaxis experienced no events during the 24-week treatment period, compared to all placebo patients developing anaphylaxis only during treatment.⁸⁵

Additionally, avapritinib enabled meaningful reductions in SDT polypharmacy, with 21% of patients reducing medication usage and 3% achieving complete SDT discontinuation versus 13% and 0% respectively in the placebo group.⁸⁶ These findings suggest avapritinib may reduce both anaphylactic episodes and treatment burden in ISM patients, though larger studies are needed to confirm these exploratory observations.

2.13.1.8 *Avapritinib reduces long-term reliance on symptom-directed therapies via improved symptom control in patients with ISM*

Downstream of avapritinib's improvement of symptom control in moderate to severe patients with ISM, clinical benefit was reported in terms of SDT usage across 2 or more classes of concomitant medications.⁸⁰ Among patients who received avapritinib for 33 months or longer, 54% had reduced the use of one or more classes of SDT and 22% had reduced their use of 2 or more classes of SDT.⁸⁰ This reduction in SDT usage is associated with lower healthcare resource utilisation equating to fewer HCP consultations and emergency visits.

2.13.2 Key findings conclusion

The PIONEER trial demonstrated that avapritinib 25 mg once daily provides sustained benefits for patients with moderate to severe ISM. The treatment showed statistically significant superiority over placebo at 24 weeks across multiple domains, including symptom burden reduction, objective measures of mast cell burden and HRQoL improvements. Long-term data from the OLE phase confirmed the durability of these treatment benefits through 3 years of follow-up, with sustained reductions in

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ISM-SAF TSS, serum tryptase levels, and *KIT D816V* VAF and favourable, long-term benefit-risk profile.⁸⁹ In terms of long-term efficacy of avapritinib, the PIONEER trial demonstrates sustained disease control and reduction in disease burden markers with avapritinib (plus SDT) alluding to a disease-modifying effect that could plausibly reduce the risk of progression to more advanced forms of disease (such as AdvSM).^{56,89} Avapritinib 25 mg once daily also demonstrated a well-tolerated safety profile comparable to placebo at 24 weeks, which remained consistent through long-term follow-up with a mean treatment duration of 37.1 months over the entire study.^{56,89} These findings support avapritinib as an effective, disease-modifying treatment option for patients with ISM who have inadequate symptom control despite optimised SDT.

2.13.3 Strengths and limitations

The PIONEER study employed a robust three-part design that enabled systematic dose optimisation, rigorous placebo-controlled efficacy evaluation and long-term safety and efficacy assessment.

The study incorporated a well-defined patient population with centrally confirmed WHO diagnosis of ISM and standardised symptom severity requirements, ensuring consistency across the trial population.⁸⁰ Baseline demographic and clinical characteristics were well-balanced between treatment groups across all parts of the study, with all enrolled participants having significant symptom burden as measured by ISM-SAF TSS, which was required for study eligibility. The PIONEER trial population is representative of UK clinical practice, with participants meeting WHO diagnostic criteria for ISM and demonstrating moderate to severe symptoms despite optimised SDT.^{31,54} UK clinical experts considered the PIONEER ITT population to be broadly generalisable to patients who would receive avapritinib in UK clinical practice, with the moderate to severe patient population representing approximately 20-30% of all ISM patients.⁴⁴

A particular strength of PIONEER was the utilisation of the ISM-SAF, a novel patient-reported outcome questionnaire specifically designed to assess ISM symptom severity and validated using data generated in this pivotal study. Given the lack of objective response criteria in ISM and the heterogeneous and subjective nature of symptom reporting, Blueprint Medicines Corporation developed this robustly Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

validated instrument that was confirmed to be appropriate for evaluation of symptom burden in ISM (refer to Section 1.3.7.1.2).^{44,52-55} The ISM-SAF enabled standardised assessment of the 11 key symptoms associated with ISM using validated 11-point scales, providing a comprehensive measure of symptom burden.⁵⁴

The randomised, double-blind, placebo-controlled design of Part 2 provided robust evidence for efficacy and safety assessments, whilst the long-term extension in Part 3 enabled evaluation of durability of treatment effects over an extended period with mean treatment duration of 37.1 months. The study demonstrated sustained efficacy across all primary and secondary endpoints through 3 years of follow-up, supporting long-term treatment benefits.⁸⁰

Several limitations should be acknowledged when interpreting the PIONEER study results. The study population was predominantly female (70.9-76.1%), under 65 years of age (84.5-93.6%) and white (77.3-85.9%).⁸⁰ While UK clinical experts agreed that the study population as representative of the intended UK treatment candidates for avapritinib, generalisability to more diverse patient populations might be limited.^{44,80}

The study design necessitated different baseline definitions for efficacy analyses in Part 3 depending on patients' treatment history, which may complicate interpretation of long-term results. For patients who received placebo in Parts 1 or 2, baseline was defined as the start of Part 3, whilst for patients who received avapritinib in Parts 1 or 2, baseline was the time of avapritinib initiation.⁸⁰

The open-label nature of Part 3 eliminates the ability to control for placebo effects in long-term efficacy assessment, though conducting long-term placebo-controlled studies in rare diseases, without standard of care and approved medical treatments, such as ISM may not be feasible or ethical given the chronic symptom burden.⁹⁰ The maintenance of objective biomarker improvements provides some mitigation of this limitation. Additionally, 50 mg dose escalation analysis in Part 3 was conducted in a subset of patients (n=71) who met prespecified clinical criteria, which may limit the generalisability of these findings to the broader ISM population.⁸⁰ It should be noted that dose escalation to 50 mg is outside the recommended marketing authorisation, which specifies a 25 mg once daily dose for ISM. While the trial protocol allowed escalation based on clinical criteria, this represents off-label use in clinical practice.¹ Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

The study excluded patients with diagnosis of other WHO systemic mastocytosis subclassifications and those with recent cytoreductive therapy, which may limit applicability to patients with more advanced disease or those who have received prior targeted therapy.⁸⁰ The requirement for specific symptom severity thresholds (ISM-SAF TSS ≥ 28) means the results may not be applicable to patients with milder symptom presentations.⁸⁰

B3 Cost effectiveness

3.1 Summary of cost-effectiveness analysis

ISM is a rare, KIT D816V-driven mast cell disease representing approximately 95% of SM cases. It is characterised by mast cell accumulation and mediator release, resulting in a wide range of heterogeneous symptoms that contribute to a substantial disease burden and impaired HRQoL. Avapritinib, a highly selective KIT D816V inhibitor, directly targets the underlying driver of disease and represents a novel treatment option for patients with moderate to severe ISM. The economic analysis therefore evaluates the cost-effectiveness of avapritinib compared to current clinical practice in England.

Alongside this submission, a patient access scheme (PAS) has been submitted with a simple fixed confidential discount of [REDACTED]. Results for PAS price have been modelled in the cost-effectiveness analysis.

Model summary:

- A *de novo* disease activity model was developed for the economic evaluation of avapritinib versus SDT in the UK, in accordance with the National Institute for Health and Care Excellence (NICE) reference case.⁹¹
- The analysis was conducted from a National Health Service/Personal Social Services (NHS/PSS) perspective, with a lifetime horizon and with costs and outcomes discounted at 3.5% per annum.⁹¹
- Efficacy data for avapritinib and the comparator were derived from the PIONEER trial (February 2025 DCO).²⁶
- Health state utility values were estimated/derived from PIONEER²⁶ for the three ISM health states, the PATHFINDER trial for AdvSM⁹², and the PRISM study for smouldering systemic mastocytosis (SSM).¹⁵
- Health state utility values were adjusted based on PRISM study evidence to account for treatment responders who remain in the same health state but were expected to experience an improvement in HRQoL.¹⁵
- The base case results showed that avapritinib was associated with substantial health benefits compared with SDT, providing an incremental 0.06 life-years (LYs) and 0.62 quality-adjusted life-years (QALYs) per patient, resulting in an incremental cost-effectiveness ratio (ICER) of £[REDACTED] per QALY gained for avapritinib versus SDT at the list price. When avapritinib is considered with a PAS confidential discount price (£[REDACTED] after a [REDACTED] reduction from Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578])

the list price), avapritinib becomes dominant versus SDT in most simulations, providing greater health benefit at lower cost, with approximately 90% probability of being cost-effective across all relevant willingness-to-pay (WTP) thresholds (£20,00-£30,000).

3.2 Published cost-effectiveness studies

- An SLR and formal critical appraisal of existing economic evaluations, and costs and healthcare resource uses were conducted in July 2025 in patients with ISM to identify relevant published cost-effectiveness studies.
- See Appendix E for full details of the process and methods used to select the cost-effectiveness studies relevant to the technology being evaluated. No economic evaluation in ISM met the inclusion criteria for the final selection of studies in the SLR (see Appendix E for excluded studies after full-text screening).

3.3 Economic analysis

The SLR of cost-effectiveness studies (detailed in Appendix E) identified no relevant economic evaluations to provide estimates for the cost-effectiveness of avapritinib in ISM.

The objective of this economic analysis was to assess the cost-effectiveness of avapritinib compared with SDT in England for patients with moderate to severe ISM.

To support this objective, a *de novo* CEM was developed, aligning with NICE committee preferences and decision-making processes in England. The model adopted three disease severity health states (mild, moderate, and severe) to represent the natural history of patients with ISM. Only a small proportion of ISM patients may progress to SSM and AdvSM, as claimed by three UK clinical experts.⁴⁴ To capture this progression, the model incorporates two tunnel health states that patients in any of the three ISM severity states can transition into. From any health state, patients may also transition to the death health state, after which the model assumes no further transitions occur.

3.3.1 Patient population

The CEM evaluates adult patients with moderate to severe ISM who are inadequately controlled on SDT. This population is consistent with both the NICE final scope and the anticipated MHRA licence indication for avapritinib, defined as

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the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment (see SmPC in Appendix A).¹

The analysis is based on the most recent PIONEER trial DCO (February 2025), incorporating clinical outcomes including changes in ISM-SAF TSS, AEs, and HRQoL,^{52-54,80} aligned with the NICE scope.⁹³

Patients from the PIONEER clinical trial were categorised into the following groups:

- Full ITT population
- Moderate to severe population
- Full ITT population without dose escalation
- Moderate to severe population without dose escalation

The moderate to severe population corresponds to the PP population, with 14 patients presenting with mild disease censored from baseline and 2 patients excluded due to protocol deviations up to the February 2025 DCO.⁸⁰

Table 37 summarises the populations and dosing regimens per-protocol.

Table 37: Patient populations selectable in the model (from February 2025 DCO)

Population of patients with ISM	Dose	Avapritinib arm	SDT alone
Full ITT population	25mg + 50mg	■	■
Moderate and severe	25mg + 50mg	■	■
Full ITT population (with dose escalation)	25mg	■	■
Moderate and severe (without dose escalation)	25mg	■	■

Abbreviations: DCO, data cut-off; ISM, indolent systemic mastocytosis; ITT, intention-to-treat; SDT, symptom-directed therapy.

Note: Full ITT population, including patients who have mild-to-moderate disease enrolled into the PIONEER trial.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).⁸⁰

This cost-effectiveness analysis focuses on the moderate to severe population without dose escalation, as this group best reflects the target population for the anticipated UK marketing authorisation. Other subgroup populations are excluded from this health economic evaluation. In line with the anticipated SmPC and validated by clinical input, the primary base case analysis considers moderate to severe ISM patients treated with avapritinib at a daily dose of 25 mg versus SDT.^{1,44} In PIONEER, some patients escalated to 50 mg and derived clinical benefit.⁸⁰

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However, since the 50 mg dose is not included in the anticipated SmPC, this higher dose was excluded from the economic base case to maintain consistency with the expected licensed indication.¹

In the economic evaluation, patients in the avapritinib arm were categorised into treatment responders and treatment non-responders. This design was to reflect the clinical trial endpoints and to capture avapritinib efficacy outcomes. Avapritinib is an orally administered therapy. Following the initial 24-week treatment period, patients who achieve a clinical response continue avapritinib at the same dose, while non-responders transition to SDT, consistent with clinical trial design and anticipated real-world practice.

3.3.2 Model perspective

The analysis was conducted from the perspective of the NHS and PSS in England and Wales (in line with the current NICE reference case).⁹¹ The cost-effectiveness analysis therefore included direct medical costs only over a lifetime horizon. All costs are reported in pounds sterling (2024/25).

3.3.3 Model structure

A *de novo* disease activity model was developed in Microsoft Excel® to accurately reflect the natural progression and clinical pathway of ISM in the UK.

As no previous economic models exist for ISM, a *de novo* CEM was developed, marking the first formal evaluation of treatment in this condition. The rarity of ISM introduces distinct methodological challenges for economic modelling, most notably the limited availability of clinical and economic evidence and the small patient cohorts included in studies to date. To address these constraints, pragmatic assumptions were required to balance feasibility with methodological rigour, ensuring that the model remained aligned with the evidence base and consistent with NICE reference case standards.⁹¹

The CEM used a trial-based model structure with three core symptom severity states (mild, moderate, severe), progression states of SSM and advanced systemic mastocytosis (AdvSM), and an absorbing state of death. Patients enter the model according to their baseline severity in PIONEER, and health state occupancy is informed directly by trial data. This approach avoids reliance on estimated transition

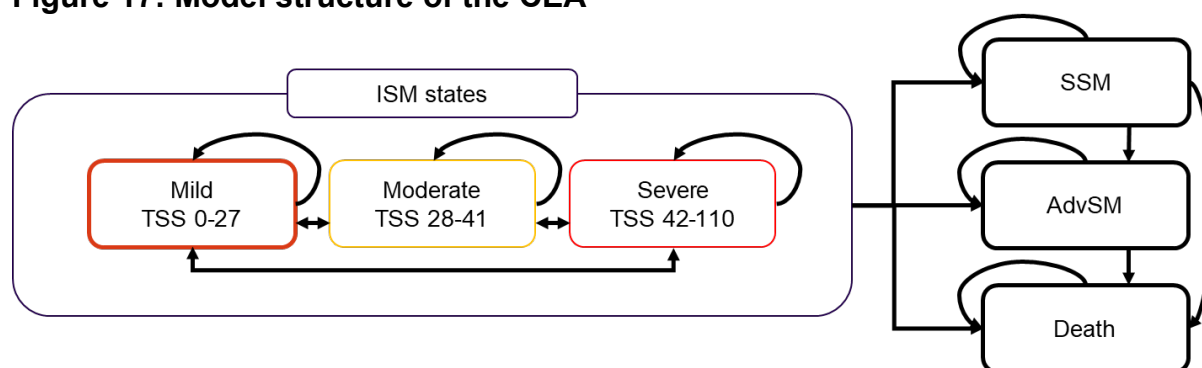
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probabilities and ensures that the analysis remains closely anchored to the observed evidence.

As noted in Section 2.4.3.2, the primary goal of treatment in ISM is symptom severity reduction. To reflect this, the CEM defines health states according to ISM severity, using baseline TSS thresholds consistent with PIONEER. Patients were categorised as mild (TSS 0–27), moderate (TSS 28–41), or severe (TSS 42–110).^{52,53,56} This ensures that the model structure captures the substantial symptom burden experienced by patients and allows differences in severity to drive both QoL and HCRU.

The inclusion of SSM and AdvSM health states recognises that, although rare, patients with ISM may progress to more advanced forms of systemic mastocytosis. Their presence in the model ensures that the natural history of the disease is represented comprehensively, even if such progression is infrequent and has limited influence on the base case results. The model structure is presented in Figure 17.

Figure 17: Model structure of the CEA



Abbreviation: AdvSM, advanced systemic mastocytosis; ISM, indolent Systemic Mastocytosis; SSM, smouldering systemic mastocytosis; TSS, total symptom score.

At the end of the initial 24-week treatment period, patients are classified as responders or non-responders according to TSS improvement criteria applied in the model. The 24-week horizon was selected based on clinical input, as this period is considered sufficient to establish whether patients derive meaningful symptomatic benefit from treatment. The primary endpoint assessment in PIONEER Part 2 was also conducted at 24 weeks, allowing responders and non-responders to be identified consistently with the trial evidence. Precedent identified in literature and clinician input indicated that a 30% improvement in TSS was the preferred definition

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of response for decision-making in practice and was therefore selected as the base case.^{44,94} A more stringent 50% improvement threshold was also tested in scenario analysis to reflect alternative interpretations of clinically meaningful benefit.

Duration of treatment (DoT) for avapritinib and SDT was informed by the US RWE and extended cohort study (ECS) data, which were used to define the proportion of patients remaining on treatment over time.⁹⁵ In the base case analysis, treatment discontinuation for avapritinib is determined by lack of response at 24 weeks, consistent with the stopping rule described above. In contrast, SDT is assumed to continue indefinitely, reflecting its role as ongoing symptomatic management for patients with ISM. Further details on DoT are provided in Section 3.4.3.1.

AEs were incorporated into the CEM where they were expected to have a meaningful impact on costs or HRQoL. Disutility was applied only for AEs whose impacts were distinct from the utility decrements already captured by the model's health state and symptom severity levels.⁵⁸ This approach avoids double-counting, as the model assumes that utility varies by disease severity rather than by treatment arm. Patients who discontinue avapritinib revert to the baseline (SDT) utility values corresponding to their health state, while additional utility losses are applied only for treatment-related AEs.

UK clinicians advised that there are no significant mortality differences between patients with mild, moderate, or severe ISM, and that symptom severity does not correlate directly with survival. Instead, mortality risk is influenced by disease burden, such as mast cell infiltration and risk of progression to AdvSM.⁹⁶ However, three clinical experts also clarified that the progression from ISM to AdvSM is rare to see in the UK clinical practice. Clinicians also confirmed that, while ISM is generally not life-limiting, patients with ISM are expected to have a higher mortality risk than the general population.⁴⁴ Hence, no mortality difference was assumed between avapritinib and SDT in the CEM. This assumption is likely conservative, as long-term treatment benefits on disease burden could plausibly translate into improved survival; however, in the absence of long-term evidence, this was treated as an uncaptured benefit.

3.3.4 Features of the economic analysis

A lifetime horizon was applied to ensure that all relevant differences in costs and outcomes between avapritinib and SDT were captured. Based on clinical expert input, the mean baseline age in the model was set at 40 years, reflecting the expected age of diagnosis in UK practice, while the mean baseline age from PIONEER (51 years) was tested in scenario analysis.⁴⁴

A cycle length of one month (28 days) was selected to align with avapritinib dosing and clinical assessments, with a half-cycle correction applied. Both costs and outcomes were discounted at 3.5% per annum as per the NICE reference case.⁹¹

In the model, treatment discontinuation was assumed to occur after [REDACTED] years (at 100 cycles). DoT was informed by US RWE due to immature discontinuation data in the PIONEER trial.^{80,95} Following discontinuation, a treatment benefit duration of three months (3 cycles) was applied, based on clinical expert input regarding the persistence of clinical benefit after stopping avapritinib.⁴⁴

The model did not assume a linear decline in treatment effect. Instead, the model used a stepwise (piecewise-deterministic) assumption, a fixed treatment wane period (3 cycles) where treatment benefit was assumed to gradually diminish to the baseline level of SDT. From cycle 102 onwards, treatment efficacy was set equal to the SDT baseline, reflecting full loss of avapritinib benefit (see Section 3.4.2 for more details).

Utilities for mild, moderate, and severe ISM were derived from EQ-5D data collected in PIONEER using the UK tariff.¹⁵ The utility for SSM was sourced from the Dutch Expert advisory board (2024)⁹⁷, while the AdvSM utility was aligned with NICE TA1012 using estimates from the PATHFINDER trial (2022).^{11,92} Utilities were age-adjusted to reflect expected declines in HRQoL with ageing, and decrements for AEs were also applied where relevant.

AEs were incorporated where they were associated with measurable costs or disutility. AE rates were derived from PIONEER, costs from NHS reference costs, and utility decrements applied only when the impact of an AE was considered distinct from the disutility captured in the underlying severity states.

Mortality was informed by published literature. The Danish study by Kibsgaard et al. (2020)²⁰ was selected as the base case, as the simulated life expectancy of patients in the model (73-75 years) was considered most appropriate following validation with UK clinical experts.⁴⁴ A more recent US study by Mukherjee et al. (2024) was explored in scenario analysis to test uncertainty.²¹ No UK-specific evidence compared to the general population was identified in the SLR conducted for this submission.

Resource use and costs were valued using NHS reference costs 2024/25 and Personal Social Services Research Unit (PSSRU) unit costs 2024.⁹⁸ Drug acquisition costs for avapritinib were based on list prices for the 25 mg dose (with PAS applied in scenario analyses, if appropriate). Symptomatic therapy and monitoring costs for SDT were derived from published UK sources and supported with clinical experts' validated assumptions. The key features of the economic analysis are described in Table 38 for ISM.

Table 38: Features of the economic analysis

Factor	Current evaluation, chosen values	Current evaluation, justification
Time horizon	Lifetime	Ensures all relevant differences in costs and outcomes are captured. Mean baseline age of 40 years used (expert input); 51 years from PIONEER tested in scenario analysis.
Discount rate	3.5% p.a. for costs and benefits	Applied to ensure consistency of costs and outcomes over time.
Cycle length	1 month (28 days)	Aligns with avapritinib dosing and trial data collection. Half-cycle correction applied.
Duration of treatment (DoT)	Based on US RWE. ⁹⁵	PIONEER data too immature to inform DoT; RWE provides a more reliable basis.
DoT benefit	3 months following discontinuation	Based on clinical expert input regarding persistence of clinical benefit after stopping avapritinib.
Source of utilities	Mild, moderate, severe: EQ-5D from PIONEER (UK tariff). ¹⁵ . SSM: Dutch Expert advisory board (2024). ⁹⁷ AdvSM: NICE TA1012, PATHFINDER trial (2022). ^{11,92} AE decrements applied from literature (see Table 53). Age-adjusted utilities using Hernández et al. (2022). ⁹⁹	Reflects trial evidence and published sources. Same utilities applied to both arms to avoid bias in absence of differential evidence.
Mortality	HRs from Kibsgaard et al. (2020) ²⁰ (base case); Mukherjee et al. (2024) ²¹ (scenario)	Kibsgaard et al. was chosen as base case because the simulated life expectancy of 73-75 years aligned with expert validation. Mukherjee et al. tested in scenario to explore uncertainty.
Adverse events	Based on PIONEER trial (rates), NHS reference costs (costs) ¹⁰⁰ , and trial-based utilities (disutility values)	AE impacts included only where distinct from severity state disutility, avoiding double-counting.
Resource use	Resource usage (see Table 58) Costs: NHS reference costs 2024/25 ¹⁰⁰ ; PSSRU unit costs 2024. ⁹⁸	Provides consistency with NHS resource use and valuation.

Abbreviations: AE, adverse event; AdvSM, advanced systemic mastocytosis; EQ-5D, EuroQoL-5 Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; SSM, smouldering SM. Note: the sources of disutility values are provided in Table 53.

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3.3.5 Intervention technology and comparators

Treatments in the model include avapritinib plus SDT compared with SDT (H1-blocker, H2-blocker, omeprazole, montelukast, prednisolone, nalcrom, omalizumab), consistent with the NICE scope. Off-label TKIs (e.g., midostaurin, imatinib, and dasatinib) were also included in the base case using EU data, as this was considered reflective of prescribing in clinical practice, despite these agents not being reimbursed for ISM in the UK. Off-label TKIs are not considered for concomitant use with avapritinib treatment but are included in the comparator arm as part of SDT when used alone. Given the limited evidence base supporting TKI use in ISM, there remains uncertainty regarding their real-world utilisation and clinical effectiveness. To address this, different proportions of TKI use were explored in scenario analyses to assess the impact of this uncertainty on the cost-effectiveness results.

NHS clinical practice is consistent with European and US guidelines for the management of ISM, where patient-specific SDT regimens are commonly used, and selected off-label therapies may be considered.^{22,68} Avapritinib is approved by the EMA for moderate to severe ISM symptoms⁹ and by the FDA for symptomatic ISM.⁸

3.3.5.1 Intervention technology: Avapritinib

The intervention of interest in the economic analysis is avapritinib, administered orally at a dose of 25 mg once daily in 28-day cycles, consistent with the anticipated UK SmPC and PIONEER trial regimen.^{1,26}

Patients receiving avapritinib are assumed to continue on concomitant SDT, but at a reduced intensity (Table 39), reflecting the expected reduction in symptomatic therapy needs with effective treatment. This assumption was validated with UK clinical experts and tested in scenario analyses.

Stopping rules in the model followed the PIONEER protocol and expected UK practice: after the initial 24-week period, responders continue avapritinib at the same dose, while non-responders discontinue avapritinib and remain on SDT alone.

3.3.5.2 Symptom-directed therapy

In the CEM, SDT was implemented as a blended basket of symptomatic therapies (Table 39). This reflects variation in clinical practice while simplifying the model

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structure. All patients in the comparator arm were assumed to remain on full SDT for the modelled duration. The model assumed that SDT therapy for treatment responders is reduced by 50%, which is based on the proportion of patients reduced by background therapy in the PIONEER trial.

Off-label TKI use was included in the base case using EU data, given that this was considered reflective of clinical practice despite a lack of reimbursement in the UK. Uptake rates were varied in scenario analyses to explore uncertainty around their contribution to current management. The model assumed the duration of TKI treatment is 2 years.

Table 39: Symptom-directed treatment basket

Comparator	Proportion of patients in avapritinib + SDT arm	Proportion of patients in SDT arm	Data source
H1-blockers (average)	97.4%	100.0%	PIONEER ^{54,80}
H2-blocker (cimetidine)	68.9%	66.0%	PIONEER ^{54,80}
PPI (omeprazole)	17.2%	28.2%	PIONEER ^{54,80}
Leukotriene inhibitor (montelukast)	37.7%	35.2%	PIONEER ^{54,80}
Corticosteroid (prednisolone)	11.9%	9.9%	PIONEER ^{54,80}
Cromolyn sodium (nalcrom)	32.5%	35.2%	PIONEER ^{54,80}
Monoclonal antibody (omalizumab)	10.6%	9.9%	PIONEER ^{54,80}
Off-label TKIs			
Midostaurin	0%	9.9%	NICE TA728 ⁷⁶
Imatinib	0%	3.3%	Expert opinion ⁴⁴ Buonomo et al. (2022) ⁷⁰
Dasatinib	0%	1.1%	Buonomo et al. (2022) ⁷⁰ Verstovsek S et al. (2008) ¹⁰¹

Abbreviations: H1/H2, antihistamines; PPI, proton-pump inhibitors; SDT, symptom-directed therapy; TKIs, tyrosine kinase inhibitors.

Note:1) UK clinicians confirmed that TKIs are rarely used in practice due to limited supporting evidence, though some use in ISM does occur.⁴⁴ 2) The average of H1-blockers used in PIONEER including desloratadine, fexofenadine, cetirizine, loratadine.

3.4 Clinical parameters and variables

Key clinical parameters in the CEM were informed by data from the PIONEER study and supplemented with external sources where necessary. The PIONEER February 2025 data cut was used for the base case. The DoT of avapritinib was supported by RWE from the US, given the immaturity of PIONEER data, meaning any parametric curves would be highly uncertain. The sources for each parameter are summarised in Table 40.

Table 40: Summary of sources of data used in the economic model

Clinical parameter	Source	Notes
Baseline characteristics	PIONEER ^{54,80}	Age = 40 years (base case); 51 years (scenario)
Efficacy (TSS states, response)	PIONEER ^{54,80}	Health state occupancy generated from trial data
Duration of treatment	US RWE DoT ⁹⁵	Stopping rules applied at ≥30% reduction at 24 weeks (base case); ≥50% in scenario Mean ToT = 2.76 years; includes AE discontinuation
Duration of treatment benefit	Clinical input ⁴⁴	3-month carryover post-discontinuation
Utilities (ISM states)	PIONEER EQ-5D ^{54,80}	Mapped to EQ-5D-3L ⁹⁹
Utilities (SSM, AdvSM)	PRISM study ¹⁵ PATHFINDER clinical trial ⁹²	PRISM and PATHFINDER (AdvSM) trial data
Utilities (age adjustment)	Hernández et al. (2022) ⁹⁹	Applied each cycle
Utilities (AE disutility)	PIONEER ^{54,80}	Applied where distinct from severity utilities
Adverse events	PIONEER (25 mg OD) ^{54,80}	Grade ≥3; costs from NHS reference costs
Mortality	Kibsgaard et al. (2020) ²⁰ Mukherjee et al. (2024) ²¹	Base case vs scenario; general pop mortality from ONS

Abbreviation: AE, adverse event; AdvSM, advanced systemic mastocytosis; DoT, duration of treatment; EQ-5D, EuroQoL-5 Dimension; HRQoL, health-related quality of life; ISM, indolent systemic mastocytosis; RWE, Real-world evidence; OD, Once daily; ONS, Office for National Statistics; ToT, time-on-treatment; TTD, time to discontinuation.

3.4.1 Baseline characteristics

The modelled cohort was generated by random sampling of baseline characteristics from PIONEER. Clinicians confirmed the distribution was representative of ISM patients in the UK.⁴⁴

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The base case applied a mean baseline age of 40 years (UK clinical input)⁴⁴; 51 years from PIONEER was tested in scenario analysis. Patients were categorised by baseline TSS into mild (0–27), moderate (28–41), and severe (42–110), with only moderate to severe patients included in the base case.

Table 41: Patient baseline characteristics used in the base case

Characteristic	PIONEER trial	Model base case	Source
Age (years, mean)	51	40	PIONEER ^{26,54} , Clinician input ⁴⁴
Male (%)	27.2%	27.2%	PIONEER ^{26,54}
Weight (kg, mean)	81.29	81.29	PIONEER ^{26,54}

Note: Model assumed patients' starting age at 40 years; the proportion of females was calculated based on the proportion of male.

3.4.2 Efficacy

Clinical response in the CEM was defined by changes in the TSS captured by the ISM-SAF(© Blueprint Medicines Corporation) tool.^{52-54,80} The response criteria for both treatment arms set in the model is assumed to be a 30% reduction in TSS changes, validated by three UK clinical experts to ensure they are clinically meaningful. The model base case assumes 10 minimum of patients required for this analysis, and the model explored 0 and 30 minimum of patients in the scenario analyses.

Patients were categorised into severity states (mild, moderate, severe) consistent with the PIONEER trial.^{26,54,80} This cost-effectiveness analysis focuses on moderate to severe patients without dose escalation, so the treatment effects of other subgroups are only presented in Appendix C.

3.4.2.1 Treatment effect of avapritinib

Health state occupancy was modelled directly from the PIONEER TSS summary report. For avapritinib, observed distributions were applied over the planned full trial follow-up (up to 252 weeks). Beyond this period, patients were assumed to remain in their current state until discontinuation, after which they transitioned to the SDT health state distribution. The health state distributions up to week 252 are presented in Table 42.

In line with SmPC, avapritinib in the treatment of ISM patients is administered at 25mg orally per day. Therefore, no dosage reduction was assumed for long-term responders in the base case.¹

Table 42: Health state distribution for moderate to severe ISM patients without dose escalation from baseline to week 252 (PIONEER trial February 2025 DCO)

Week	Mild	Moderate	Severe
Baseline	■	■	■
Week 4	■	■	■
Week 8	■	■	■
Week 12	■	■	■
Week 16	■	■	■
Week 20	■	■	■
Week 24	■	■	■
Week 28	■	■	■
Week 32	■	■	■
Week 36	■	■	■
Week 40	■	■	■
Week 44	■	■	■
Week 48	■	■	■
Week 52	■	■	■
Week 56	■	■	■
Week 60	■	■	■
Week 64	■	■	■
Week 68	■	■	■
Week 72	■	■	■
Week 76	■	■	■
Week 80	■	■	■
Week 84	■	■	■
Week 88	■	■	■
Week 92	■	■	■
Week 96	■	■	■
Week 100	■	■	■
Week 104	■	■	■
Week 108	■	■	■
Week 112	■	■	■
Week 116	■	■	■
Week 120	■	■	■
Week 124	■	■	■
Week 128	■	■	■
Week 132	■	■	■
Week 136	■	■	■

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Week	Mild	Moderate	Severe
Week 140	■	■	■
Week 144	■	■	■
Week 148	■	■	■
Week 152	■	■	■
Week 156	■	■	■
Week 160	■	■	■
Week 164	■	■	■
Week 168	■	■	■
Week 172	■	■	■
Week 176	■	■	■
Week 180	■	■	■
Week 184	■	■	■
Week 188	■	■	■
Week 192	■	■	■
Week 196	■	■	■
Week 200	■	■	■
Week 204	■	■	■
Week 208	■	■	■
Week 212	■	■	■
Week 216	■	■	■
Week 220	■	■	■
Week 224	■	■	■
Week 228	■	■	■
Week 232	■	■	■
Week 236	■	■	■
Week 240	■	■	■
Week 244	■	■	■
Week 248	■	■	■
Week 252	■	■	■

Abbreviations: ISM, indolent systemic mastocytosis.

Note: Mild, moderate, severe refers to ISM health states used in the economic model.

Source: Health state distributions from baseline to week 252 were derived from the PIONEER trial.^{26,54,80}

3.4.2.2 Treatment effect of SDT

For the SDT arm, health state occupancy data were available only up to 24 weeks, after which patients in the clinical trial crossed over to avapritinib. In the model, SDT patients were therefore assumed to return to their baseline health state distribution beyond 24 weeks. Clinical experts confirmed that this assumption was appropriate, as patients would not be expected to transition between disease severity states in the absence of a change in treatment.⁴⁴

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The health state distribution for the SDT arm, including the 24-week trial period and the subsequent 24-week waning period, is presented in Table 43 for patients with moderate to severe ISM. The SDT arm was not affected by dose escalation, consistent with clinical practice and the trial design.

Table 43: Health state distribution for moderate to severe ISM patients from baseline to week 48 – PIONEER trial (February 2025 DCO)

Week	Mild	Moderate	Severe
Baseline	■	■	■
Week 4	■	■	■
Week 8	■	■	■
Week 12	■	■	■
Week 16	■	■	■
Week 20	■	■	■
Week 24	■	■	■
Week 28	■	■	■
Week 32	■	■	■
Week 36	■	■	■
Week 40	■	■	■
Week 44	■	■	■
Week 48	■	■	■

Abbreviations: ISM, indolent systemic mastocytosis; SDT, symptom-directed therapy. Note: Mild, moderate, severe refers to ISM health states used in the economic model.

Source: Health state distributions from baseline to week 24 were derived from the PIONEER trial^{26,54,80}; treatment waning was assumed after [REDACTED] in the model.

3.4.2.3 Probability of progression

Table 44 presents transition probability from ISM health states to SSM and AdvSM health states. ISM mild states are assumed to be a quarter of the probability, and ISM moderate states to be half of the probability of severe to SSM and AdvSM. For ISM severe patients, the transition probability was calculated averages based on data from three publications, which are the ECNM registry-based study, Spanish Network on Mastocytosis (REMA) 2009 study, and REMA 2013 study.^{17,37,102}

Table 44: Probability of progression per cycle

Health states	SSM	AdvSM	Death	Assumption
ISM Mild	0.008%	0.014%	N/A	Assumption: assumed to be quarter of probability of severe to SSM and AdvSM
ISM Moderate	0.016%	0.027%	N/A	Assumption: assumed to be half of probability of severe to SSM and AdvSM
ISM Severe	0.031%	0.054%	N/A	Trizuljak et al. (2020) ¹⁷ ; Escribano et al. (2009) ¹⁰² ; Matito et al. (2013) ³⁷
SSM	N/A	0.168%	0.000%	Trizuljak et al. (2020) ¹⁷ ; Escribano et al. (2009) ¹⁰² ; Matito et al. (2013) ³⁷ SSM to death is assumption
AdvSM	N/A	N/A	0.000%	Assumption

Abbreviations: AdvSM, advanced systemic mastocytosis; ISM, indolent SM; N/A, not applicable; SSM, smouldering SM. Note: as per UK clinical experts' advice, the ISM patients assumed no difference in mortality with the general population, therefore, the mortality rates are assumed to be the same as the data obtained from ONS (2024/2025).^{44,103} The transition probability to death per cycle is too minor to be captured in this table.

3.4.3 Methodology for health state summaries

Patient-level data were summarised by cycle (4-week intervals) using the first day's visit score as the representative value. No imputation was applied; patients with missing observations were excluded for that cycle.

Patients with mild ISM at baseline were excluded from the analysis, as the anticipated licence for avapritinib restricts use to moderate to severe ISM inadequately controlled on SDT.¹ Similarly, patients who received dose escalation were excluded, ensuring the analysis reflects only the licensed 25 mg dose. These exclusions ensured the CEM remained aligned with the intended target population and dosing regimen, while acknowledging that escalation and mild patients were present in PIONEER.^{26,54,80}

3.4.3.1 Duration of treatment benefit

The PIONEER trial provided limited information on long-term time to discontinuation (TTD), as only a small number of patients had discontinued treatment by the latest data cut. This meant the trial data were not mature enough to generate reliable extrapolations to inform the DoT benefit without introducing extreme uncertainty. To address this, US RWE was used to inform TTD, as it provided a broader evidence base with sufficient discontinuation events to support robust modelling.⁹⁵ The RWE

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cohort included 864 SM patients with a starting dose of 25mg as a proxy for identifying ISM patients, treated through a speciality pharmacy and enrolled in a patient assistance programme (PAP).⁹⁵

Parametric models were fitted to the US RWE TTD data,⁹⁵ with observed Kaplan–Meier (KM) estimates showing 87.1% of patients remained on treatment at 3 months, 68.8% at 12 months, and 59.4% at 24 months. Extrapolated results are presented in Table 45.

Table 45: Proportion of patients continuing treatment at landmark timepoints

Distribution	Median (months)	Mean (months)	Survival 3 months	Survival 24 months	Survival 48 months	Survival 96 months
KM						
Exponential						
Weibull						
Gompertz						
Log Normal						
Log Logistic						
Gamma						
Generalised Gamma						

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan Meier; N/A, not applicable. Source: In the absence of UK long-term efficacy data, survival analysis outputs for long-term extrapolation were generated using US real-world data (n=864).⁹⁵

Table 46: AIC/BIC statistics for parametric curves

Distribution	AIC	BIC	Average AIC and BIC
Exponential	2461.21	2465.97	2463.59
Weibull	2441.23	2450.75	2445.99
Gompertz	2417.87	2427.39	2422.63
Log Normal	2412.31	2421.83	2417.07
Log Logistic	2429.14	2438.66	2433.90
Gamma	2445.50	2455.02	2450.26
Generalised Gamma	2406.49	2420.77	2413.63

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Although the generalised gamma distributions demonstrated the best statistical fit (lowest AIC/BIC), it projected implausibly high long-term persistence with a mean DoT of 31.7 years, inconsistent with clinical expectations. Given the large degree of uncertainty still present in the extrapolated parametric curves, an average DoT was

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taken excluding the two clinically implausible extrapolations (Gompertz and Generalised Gamma; mean DoTs of [REDACTED] years respectively). This resulting in an average DoT of [REDACTED] years. A secondary scenario was tested, averaging the parametric extrapolations except Gompertz, which resulted in a mean DoT of [REDACTED] years. Clinician input was gathered for a previous DoT analysis (conducted using a 12-month data cut of the US RWE dataset on n=375 patients) with which consensus identified DoT extrapolations resulting in average DoTs between 8 and 11 years as what would be expected in clinical practice, however, also asserting that there remains significant uncertainty regarding long-term avapritinib usage for such long durations of time.⁴⁴ Therefore, the mean DoT of [REDACTED] years was determined to be a safe assumption for the length of treatment for avapritinib patients, with an optimistic long-term treatment scenario of [REDACTED] included as a scenario.

Figure 18: 240-month extrapolations for TTD



Abbreviation: TTD, time to discontinuation. Note: the graph was extrapolated using US real-world evidence data.⁹⁵

3.4.3.2 Stopping rule and treatment response

A stopping rule was applied in the model to reflect clinical practice and trial design. At six months (cycle 6), patients were assessed for treatment response, consistent with the length of Part 2 of PIONEER. The model allowed two alternative thresholds for defining response: a 30% or 50% reduction in TSS. Patients meeting the chosen Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

threshold were assumed to continue treatment with avapritinib, while non-responders discontinued avapritinib and switched to SDT alone.

The base case applied the 30% reduction in TSS, in line with the criteria recommended by the European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) consortium.⁹⁴ Scenario analyses explored the impact of applying a 50% reduction. Table 47 presents the response rates by severity category in the moderate to severe population of PIONEER.

Table 47: Avapritinib responders in the moderate to severe no dose escalation

Start cycle	Response criteria	Mild (n)	Moderate (n)	Severe (n)	Proportion of patients meeting criteria	Reference
1 (baseline)	–	■	■	■	100% (n=■)	PIONEER post-hoc analysis*
7	≥30% TSS reduction	■	■	■	52.5% (n=■)	PIONEER post-hoc analysis*
7	≥50% TSS reduction	■	■	■	30.0% (n=■)	PIONEER post-hoc analysis*

Abbreviations: TSS, total symptom score. Note: *Moderate to severe no dose escalation population (n=85) from the February 2025 data cut.⁸⁰ Proportions calculated for CEM inputs based on number of responders per severity state.

3.4.3.3 Discontinuation due to adverse events

In addition to non-response, discontinuation could also occur due to AEs. Consistent with the PIONEER safety population, ■ of patients in the avapritinib arm were assumed to discontinue during the first treatment cycle due to AEs. For SDT, the discontinuation rate was assumed to be 0%, as clinicians indicated that SDT adjustments due to AEs rarely lead to complete treatment discontinuation. These assumptions align with observed trial data.^{54,80}

3.4.3.4 Summary of DoT

DoT estimates incorporated both response-based continuation and AE-related discontinuation. These values informed the model inputs for treatment persistence (Table 48).

Table 48: Time-on-treatment data used in the model

Parameter	Value	Source
TTD	██████	US RWE TTD data, with observed KM estimates. ⁹⁵
Response rate ($\geq 30\%$ TSS)	48.0%	PIONEER ITT, June 2022 CSR. ⁵⁴
Response assessment timepoint	24-weeks	PIONEER ITT, June 2022 CSR. ⁵⁴
AE discontinuation rate	██████	PIONEER safety, 2024 CSR. ¹⁰⁴
AE discontinuation timepoint	24-weeks	PIONEER safety, 2024 CSR. ¹⁰⁴
Long-term treatment efficacy	Treatment waning to SDT	Clinical expert opinion. ⁴⁴
Duration of treatment waning (cycles)	██████	Assumption
Proportion of patients who maintain response	0.0%	Assumption
Reduced dose for long-term responders	No	Assumption

Notes: ToT inputs based on PIONEER safety population, including patients with dose escalation (n=125).

Abbreviation: AE, adverse event; ITT, intention-to-treat; KM, Kaplan–Meier; SDT, symptom-directed therapy; TTD, time to discontinuation; ToT, time-on-treatment.

3.4.4 Adverse events

The incidences of AEs included in the model were based on Grade 3–4 events reported in the PIONEER trial.²⁶ For simplicity, AEs were modelled as one-off events occurring in the first cycle only. This assumption reflects their limited overall impact on cost-effectiveness outcomes and the fact that patients experiencing significant toxicity were already captured via discontinuation inputs.

Each AE was assigned a once-off cost, based on NHS reference sources, and a disutility value, informed by published literature. The total AE-related costs and disutilities were calculated by multiplying the incidence of each AE by its associated unit cost and disutility. Anaphylaxis was modelled separately using data from the PRISM study, with higher incidence assumed under SDT and a reduced risk applied for avapritinib (see Table 49).

Table 49: Adverse events incidence

Adverse event	Avapritinib	SDT	Reference
Headache	7.8%	9.9%	PIONEER data tables*
Nausea	6.4%	8.5%	PIONEER data tables*
Oedema peripheral	6.4%	1.4%	PIONEER data tables*
Periorbital oedema	6.4%	2.8%	PIONEER data tables*
Fatigue	4.3%	2.8%	PIONEER data tables*

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Adverse event	Avapritinib	SDT	Reference
Flushing	4.3%	0.0%	PIONEER data tables*
Alopecia	3.5%	4.2%	PIONEER data tables*
Blood ALP increased	3.5%	0.0%	PIONEER data tables*
Contusion	3.5%	0.0%	PIONEER data tables*
Eyelid oedema	3.5%	1.4%	PIONEER data tables*
Face oedema	3.5%	0.0%	PIONEER data tables*
AST increased	2.8%	1.4%	PIONEER data tables*
Diarrhoea	2.8%	2.8%	PIONEER data tables*
Dizziness	2.8%	7.0%	PIONEER data tables*
Hair colour changes	2.8%	1.4%	PIONEER data tables*
Photosensitivity reaction	2.8%	0.0%	PIONEER data tables*
ALT increased	2.1%	1.4%	PIONEER data tables*
Blood LDH increased	2.1%	0.0%	PIONEER data tables*
Dry mouth	2.1%	1.4%	PIONEER data tables*
Muscle spasms	2.1%	0.0%	PIONEER data tables*
Anaphylaxis without complications	12.3%	25.5%	PRISM study^

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; SDT, symptom-directed therapy.

Sources: *PIONEER full data^{26,54,80}; Treatment-Related Adverse Events by Preferred Term (n≥3); ^PRISM study: 51% report ≥1 anaphylaxis reaction per year. Assumed that results in 25.5% having anaphylaxis with complications, 25.5% without complications. Assumed incidence in avapritinib arm to be halved compared to SDT.

3.4.5 Mortality

All-cause mortality rates specific to age and sex were applied in each cycle using UK Office for National Statistics (ONS) life tables.¹⁰³ This ensured modelled survival did not exceed that of the general population and corrected for unrealistic long tails from parametric extrapolations.

Clinician input confirmed that mortality in ISM does not vary by symptom severity, as symptom burden does not directly correlate with survival.⁴⁴ Instead, mortality is driven by disease biology, including mast cell infiltration and the risk of progression to AdvSM. Accordingly, no differential mortality by severity state was applied.

UK clinicians indicated that ISM patients typically have shorter life expectancy than the general population, with most surviving into their 70s and few seen into their 80s.⁴⁴ This aligns with published literature showing elevated mortality risk relative to age-matched controls.²⁰

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To quantify this risk, HRs from the literature were applied to general population mortality (Table 50). Kibsgaard et al. (2020) reported an HR of 2.06, while Mukherjee et al. (2024) reported an HR of 1.53.^{20,21} Following validation with UK clinicians, Kibsgaard was selected for the base case as more representative of observed practice, while Mukherjee was explored in scenario analysis.

Table 50: Hazard ratios of mortality by health state vs the general population

Health state	HR vs general population	Source
ISM: Mild	2.06	Kibsgaard et al. (2020) ²⁰
ISM: Moderate		
ISM: Severe		
SSM	5.50	Tefferi et al. (2019) ¹⁰⁵
AdvSM		

Abbreviations: AdvSM, advanced SM; HR, hazard ratio; ISM, indolent SM; SM, systemic mastocytosis; SSM, smouldering SM.

Increased malignancy risk has been observed in ISM patients, contributing to earlier mortality. Although avapritinib may plausibly reduce mast cell burden and improve survival, current evidence is insufficient to model a treatment-related mortality benefit. This unmodelled effect represents a conservative assumption.

3.5 Measurement and valuation of health effects

3.5.1 Health-related quality of life data from clinical trials

As described in Section 2.7.4, HRQoL was collected in the PIONEER trial using EQ-5D.²⁶ As per the study protocol, assessments for both questionnaires in PIONEER were scheduled to occur at baseline and at the end of week 24.

Table 51: EQ-5D (PIONEER) Utility values by disease severity

Disease category	Changes in utility values	Utility values	Source
Mild			Estimate from PIONEER trial EQ-5D data. ^{26,54,80}
Moderate			
Severe			
SSM			Estimation based on the Dutch Expert Advisory Board. ⁹⁷
AdvSM			AdvSM progressed 1L, PATHFINDER trial EQ-5D data. ⁹²

Abbreviations: 1L, first-line; AdvSM, advanced systemic mastocytosis; EQ-5D, EuroQoL-5 Dimension; SSM, smouldering SM.

Utility values were applied to each ISM severity state (mild, moderate, severe) as well as the SSM and AdvSM health states. These utility values for these different states were assumed to be independent of the treatment administered to patients. In the PIONEER clinical trial and PRISM study, utility values were estimated for each TSS category.^{15,26} In the PIONEER trial, EQ-5D data was not collected for SSM and AdvSM, so EQ-5D data from the best available alternate source was used (as per NICE reference case). In this case SSM health state utility was based on Dutch Expert advisory board, and AdvSM utility value was elicited from the NICE TA1012 and PATHFINDER trial.^{11,92,97}

3.5.2 Health-related quality of life studies

An SLR was performed to identify relevant HRQoL data for incorporation into the model. The searches were conducted in July 2025, and comprehensive details of the SLR search strategy, study selection and results are provided in Appendix F.

Of 48 publications screened in full-text, 17 studies were included in the SLR after removing duplication. All of these identified studies were related to the PIONEER trial as summarised in Table 51. As a result, none of these studies provided additional HRQoL evidence that could be used to inform the health economic model.

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3.5.3 Utility adjustments based on response

Based on Dutch clinical expert input and the definition of mild, moderate, and severe disease, it is possible for avapritinib responders ($\geq 30\%$ reduction in TSS) to experience clinically meaningful symptom improvement without transitioning to a less severe health state.⁹⁷ Therefore, such improvement would likely translate into higher HRQoL.⁹⁷ As shown in Table 52, the model applies an improved HRQoL for avapritinib patients who achieve the TSS response threshold and remain in the severe health state. As part of the base case, these patients achieved 50% of the HRQoL improvement of the increment between the moderate and severe health states (██████████).

Table 52: Response adjustment to utility values

Adjust the utility for the response	Utility increment
Increase utility of severe responders by	██████████

Note: Adjust utility values for patients who respond to treatment, but do not move health state

3.5.4 General population utility value

The study applies age- and sex-specific utility values from the general UK population, as reported by Hernández et al. (2022), to adjust cohort utilities for ageing, in line with Technical Support Document (TSD) 12 from the NICE Decision Support Unit (DSU) on the use of health state utility values.^{99,106} To capture this effect over the model time horizon, an index-based age adjustment is applied to the utility values for each disease category.

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 QoL due to the AEs. Each disutility value was corrected for the cycle probability and the duration of the corresponding adverse event. To inform the model, both published literature and UK clinician opinions were used, as reported in Table 53.⁴⁴ Some of the AEs were grouped under a single definition. In this case, an aggregate disutility value and an aggregate AE duration were calculated by taking the average.

Table 53: Disutility values of Grade 3+ AEs

Adverse event	Disutility	Reference	Duration (days)	Comments
Headache	0.0266	Sullivan et al. ¹⁰⁷	14.00	Duration of 14 days for all AEs assumed to be the same as the AdvSM
Nausea	0.1360	Araujo et al. ¹⁰⁸	14.00	-
Oedema peripheral	0.1240	NICE TA423. ¹⁰⁹	14.00	Assumed disutility for oedema
Periorbital oedema	0.1240	NICE TA423. ¹⁰⁹	14.00	Assumed disutility for oedema
Fatigue	0.1150	Lloyd et al. ¹¹⁰	14.00	-
Flushing	0.0669	Sullivan et al. ¹⁰⁷	14.00	Assume disutility for anxiety
Alopecia	0.0400	NICE TA124. ¹¹¹	14.00	-
Blood ALP increased	0.0900	NICE TA192. ¹¹²	14.00	-
Contusion	0.0000	-	-	-
Eyelid oedema	0.1240	NICE TA423. ¹⁰⁹	14.00	Assumed disutility for oedema
Face oedema	0.1240	NICE TA423. ¹⁰⁹	14.00	Assumed disutility for oedema
AST increased	0.0900	NICE TA192. ¹¹²	14.00	-
Diarrhoea	0.1260	Araujo et al. ¹⁰⁸	14.00	-
Dizziness	0.1200	NICE CG173. ¹¹³	14.00	-
Hair colour changes	0.0669	Sullivan et al. ¹⁰⁷	14.00	Assume disutility for anxiety
Photosensitivity reaction	0.0000	-	-	-
ALT increased	0.0900	NICE TA192. ¹¹²	14.00	-
Blood LDH increased	0.0900	NICE TA192. ¹¹²	14.00	-
Dry mouth	0.0000	-	-	-
Muscle spasms	0.0700	Farkouh et al. ¹¹⁴	14.00	-
Anaphylaxis without complications	0.0900	Shaker et al. ¹¹⁵	14.00	-
Anaphylaxis with complications	0.1800	Assumed double anaphylaxis without complications.	14.00	-

Abbreviations: AdvSM, advanced systemic mastocytosis; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase.

3.5.6 Decrement in utility associated with mode of administration

Feedback from UK clinicians suggests omalizumab is administered subcutaneously.⁴⁴ Due to the lack of data/the limited use of omalizumab (9.9% of product prescription) in the UK clinical setting as shown in Table 39, the economic model did not explore the disutility associated with subcutaneous administration or the benefit associated with the availability of an oral treatment over existing treatments. Therefore, this remains an uncaptured benefit in the model.

3.6 Cost and healthcare resource use identification, measurement and valuation

An SLR was performed to identify relevant cost and healthcare resource data for incorporation in the model. The searches were conducted in July 2025, and comprehensive details of the SLR search strategy, study selection and results are provided in Appendix G.

In total, 8 cost and resource use studies from 10 publications were included in the SLR after full-text screening and duplication. All 6 studies were carried out in the United States, one study was carried out across European countries, and one study was not reported. Therefore, limiting their applicability to clinical practice in England. As a result, no data from these studies were used in the economic analysis.

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 2025 UK pounds. Where necessary, costs were inflated to 2024/25 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 PSSRU.¹⁰⁰

3.6.1.1 Drug acquisition costs of intervention and comparators

The recommended dose of avapritinib is 25 mg orally once daily. Avapritinib is available in 25 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]

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discount off the list price, has been submitted to NHS England in line with the existing PAS discount from AdvSM appraisal.¹¹

Drug acquisition costs for avapritinib and a basket of SDT drugs included in this economic evaluation are summarised in Table 54. The average breakdown of H1-blockers used in the analysis are presented in Table 55. Drug costs for the basket of SDT were taken from eMIT 2024/2025, where possible, as this is the most representative source of costs for treatments available, with treatments unavailable within eMIT taken from the British National Formulary (BNF).^{10,116}

Table 54: Summary of drug acquisition cost per cycle

Drug costs	Dose per syringe/ tablet (mg or mg/ml)	Units per package	Cost per package	Discount	Cost per mg / ml	Cost per cycle	Reference
Avapritinib	25 mg	30	£26,667.00	0%	£35.56	£24,889.20	BNF 2025 ¹⁰
Avapritinib	25 mg	30					
H1-blockers (average)	36.25 mg	30	£0.82	0%	£0.001		Calculated average; eMIT 2024/25;
H2-blocker (cimetidine)	400 mg	60	£4.52	0%	£0.000		eMIT 2024/25 (DAC042)
Proton-pump inhibitor (omeprazole)	20 mg	28	£0.41	0%	£0.001		eMIT 2024/25 (DAI012); (Omeprazole 20mg/capsules)
Leukotriene inhibitor (montelukast)	10 mg	28	£0.76	0%	£0.003		eMIT 2024/25 (DC D052)
Corticosteroids (prednisolone)	5 mg	28	£0.52	0%	£0.004		eMIT 2024/25 Calculated the average: (DFN040+DFC025)/2
Cromolyn sodium (Nalcrom)	100 mg	100	£84.22	0%	£0.008		NHSBSA(https://dmd-browser.nhs.uk/a/mpp/view/186870?ref=)
Monoclonal antibodies (omalizumab)	150 mg / 1 ml	1	£256.15	0%	£1.708		BNF 2025-Part VIIIA Category C
Midostaurin	25 mg	56	£5,609.94	0%	£4.007		BNF 2025 - Rydapt 25mg capsules
Imatinib	100 mg	60	£333.41	0%	£0.056		BNF 2025 - 100mg tablets

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Dasatinib	20 mg	60	£650	0%	£0.05 42		BNF 2025 - Dasatinib 20mg tablets

Abbreviations: H1/H2 blocker, antihistamines; BNF, British National Formulary; eMIT, electronic market information tool.

Sources: British National Formulary¹¹⁷ ; eMIT database¹¹⁶

Table 55: H1-blockers used in the analysis

H1-blockers	Dose per syringe/ tablet (mg or mg/ml)	Units per package	Recommended dose per administration	Price per pack	Source
Desloratadine	5 mg	30	5 mg	£1.73	eMIT 2023-25 (DCD058)
Fexofenadine	120 mg	30	120 mg	£0.88	eMIT 2023-25 (DCD042)
Cetirizine	10 mg	30	10 mg	£0.39	eMIT 2023-25 (DCD008)
Loratadine	10 mg	30	10 mg	£0.29	eMIT 2023-25 (DCD031)
Averages	NA	NA	36 mg	£0.82	Calculated

Abbreviations: eMIT, electronic market information tool.

Source: eMIT database.⁴⁴

The dosing schedule assumed for treatments included in the economic model is presented in Table 56. These schedules were informed by the respective SmPCs and discussions with UK clinical experts.⁴⁴ The proportion of the product prescribed in both the avapritinib and the SDT alone arm is shown in Table 39.

Table 56: Dosing schedule

Treatment	Administration route	Recommended dose per administration	Dosing frequency	Units per administration
Avapritinib ¹¹⁸	Oral	25 mg	Once daily	1
H1-blocker (average) ¹¹⁹⁻¹²²	Oral	36 mg	Once daily	1
H2-blocker (cimetidine) ¹²³	Oral	400 mg	Once daily	1
Proton-pump inhibitor: omeprazole ¹²⁴	Oral	20 mg	Once daily	1
Leukotriene inhibitor: montelukast ¹²⁵	Oral	10 mg	Once daily	1
Corticosteroids: prednisolone ¹²⁶	Oral	5 mg	Once daily	1

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Treatment	Administration route	Recommended dose per administration	Dosing frequency	Units per administration
Cromolyn sodium: nalcrom ¹²⁷	Oral	100 mg	Once daily	1
Monoclonal antibodies: omalizumab ¹²⁸	SC	150 mg / 1 ml	Every 4 weeks	1
Midostaurin ¹²⁹	Oral	200 mg	100 mg twice daily	8
Imatinib ¹³⁰	Oral	400 mg	Once daily	4
Dasatinib ¹³¹	Oral	100 mg	Once daily	5

Abbreviations: H1/H2 blocker, antihistamines; BNF, British National Formulary; eMIT, electronic market information tool; SC, subcutaneous.

3.6.1.2 Administration costs of intervention and comparators

All treatments in the model excluding omalizumab are oral therapies. Therefore, it was assumed there would be no administration costs associated with these treatments. Omalizumab is administered through subcutaneous injection. Therefore, a cost of administration representing the cost of a 30-minute appointment with a Band 6 nurse was determined to be representative. The cost of the Band 6 nurse appointment was sourced from the lasted PSSRU published costs.⁹⁸

Table 57 summarises the costs of the administration procedures. A one-off training cost by the Band 6 qualified nurse for subcutaneous administration was applied to all patients at the first cycle of the model.

Table 57: Drug administration costs

Administration route	Unit cost	Reference
Subcutaneous (SC)	£32.00	The cost of a 30-minute contact with a Band 6 nurse is calculated using the hourly cost (£64) from the PSSRU 2024/25 Manual (Section 9.2. Annual and unit costs for qualified nurses) ⁹⁸
Oral	£0.00	Assumption

Abbreviations: PSSRU, Personal Social Services Research Unit.

Source: PSSRU (2024/2025)⁹⁸ PSSRU unit cost drawn on NHS England's National Cost Collection 2023/2024, costs inflated to 2024/2025.

3.6.2 Health-state unit costs and resource use

A Dutch advisory board was consulted regarding an estimate for the frequency and nature of resource utilisation in patients with ISM, distinguishing between those

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patients who had underlying different disease activities.⁹⁷ Following their input, the level of resource usage would be determined largely by the level of disease severity in ISM along with a prediction of a further reduction in the required number of specific procedures for patients who respond to avapritinib (see Table 59). This reduction in resource use for responders is assumed to be applied one year following treatment start. The SSM and AdvSM patients are assumed to have the same frequency of resource use as the severe health state.

The base frequency of resource use for the non-responder is summarised in Table 58. For treatment responders, Table 59 presents the proportional resource use reduction based on the Dutch Advisory Board as well as the calculated resource usage.⁹⁷ A value of 100% indicates no reduction.

Table 60 presents the unit costs for these resources, based on data from the National Schedule of Reference Costs, the PSSRU, and relevant technology appraisal (TA) documents where required.^{98,100}

Table 58: Resource use activity by health state (non-responder)

Resource use activity	Mild	Moderate	Severe	Reference
Gastrointestinal domain: outpatient consultation	0.26	0.31	0.32	1 visit every 12 weeks. NICE TA708 [Digestive tract conditions] ¹³²
Skin domain: Dermatology outpatient consultation	0.36	0.43	0.45	6.09 visits per year for non-responder. NICE TA534 [Eczema] ¹³³
Skin domain: Dermatologist nurse visit	0.03	0.04	0.04	0.55 visits per year for non-responder. NICE TA534 [Eczema] ¹³³
Neurologic domain: outpatient consultation	0.66	0.79	0.83	0.86 per 4 weeks for non-responders. NICE TA753 [Epilepsy] ¹³⁴
A&E visit	0.01	0.01	0.01	0.09 per year. NICE TA534 [Eczema] ¹³³
Hospitalisation	0.01	0.01	0.01	0.12 per year. NICE TA534 [Eczema] ¹³³
Day case admission	0.01	0.01	0.02	0.021 per anno. NICE TA534 [Eczema] ¹³³
Anaphylaxis without complications	0.12	0.14	0.15	PRISM study. Mean anaphylaxis 4.1. It is assumed that there 50% of these are with complications and 50% are without complications ¹⁵

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Resource use activity	Mild	Moderate	Severe	Reference
Anaphylaxis with complications	0.12	0.14	0.15	PRISM study. Mean anaphylaxis 4.1. It is assumed that there 50% of these are with complications and 50% are without complications. ¹⁵
EpiPen use	0.06	0.07	0.07	Assumption 1 per year
Bone marrow biopsy	0.29	0.35	0.37	NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] ¹³⁵
ECG	0.12	0.14	0.15	Assumed same as CT scan
Haematology visit	0.24	0.28	0.30	NICE TA778 - Blood condition [paroxysmal nocturnal haemoglobinuria] ¹³⁶ NICE TA778 - Blood condition [paroxysmal nocturnal haemoglobinuria];4 visits per year for non-responder. ¹³⁶ NICE TA778 - Blood condition [paroxysmal nocturnal haemoglobinuria] ¹³⁶
Biochemistry test: renal - Urea and electrolytes test (UE test)	0.24	0.28	0.30	NICE [TA838]; 4 per year - Blood condition, distal renal tubular acidosis. Non-responder value ¹³⁷
Coagulation test	0.31	0.37	0.39	NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] ¹³⁵ NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma]; ¹³⁵
Serum chemistry tests	0.31	0.37	0.39	NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] ¹³⁵ NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma];0.38 per cycle; cycle length:28 days ¹³⁵
Photography	0.00	0.00	0.00	NICE TA814 - Eczema [0.06 per year] ¹³⁸
CT scan	0.12	0.14	0.15	NICE [TA838]; 2 per year - Blood condition, distal renal tubular acidosis. Non-responder value ¹³⁷
Chest X-ray	0.06	0.07	0.07	Assumed to be same as ultrasound

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Resource use activity	Mild	Moderate	Severe	Reference
Ultrasound scan	0.06	0.07	0.07	NICE [TA838] - Blood condition, distal renal tubular acidosis. Non-responder value ;1 per year ¹³⁷
MRI scan	0.12	0.14	0.15	Assumed same as CT scan
Full blood count	0.24	0.28	0.30	NICE TA814 ¹³⁸ - Eczema [4 per year] & same as NICE [TA838] - Blood condition, distal renal tubular acidosis. ¹³⁷
Bone densitometry	0.03	0.04	0.04	NICE [TA838]; 0.5 per year - Blood condition, distal renal tubular acidosis. Non-responder value ¹³⁷

Note: these RUs are applied to all patients in the initial treatment period and for non-responders only in the maintenance period. Abbreviations: A&E, accident and emergency; CT, computerised tomography; ECG, electrocardiogram.

Table 59: Resource use activity by health state (responder)

Resource use activity	Proportional reduction for responders versus non-responders ⁹⁷	Mild	Moderate	Severe
Gastrointestinal domain: outpatient consultation				
Skin domain: Dermatology outpatient consultation				
Skin domain: Dermatologist nurse visit				
Neurologic domain: outpatient consultation				
Accident & Emergency visit				
Hospitalisation				
Daycase admission				
Anaphylaxis without complications				
Anaphylaxis with complications				
Epipen use				
Bone marrow biopsy				
ECG				
Haematology visit				
Biochemistry test: renal - Urine test				

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Resource use activity	Proportional reduction for responders versus non-responders ⁹⁷	Mild	Moderate	Severe
Coagulation test	■	■	■	■
Serum chemistry tests	■	■	■	■
Photography	■	■	■	■
CT scan	■	■	■	■
Chest X-ray	■	■	■	■
Ultrasound scan	■	■	■	■
MRI scan	■	■	■	■
Full blood count	■	■	■	■
Bone densitometry	■	■	■	■

Note: These RUs are applied to all patients in the initial treatment period and for responders only in the maintenance period. Abbreviations: A&E, accident and emergency; CT, computerised tomography; ECG, electrocardiogram. Proportional reduction of resource use activities for responders was sourced from the Dutch Advisory Board ⁹⁷

Table 60: Healthcare resource consumption and costs

Resource use activity	Unit cost	Reference
Abdominal pain	£129.43	Non-consultant-led outpatient (£129; PSSRU 2024/25) + paracetamol 500 mg × 4 (eMIT 2024–25)
Nausea	£182.00	NICE TA728 (£182) (2020). https://www.nice.org.uk/guidance/ta728/evidence/appraisal-consultation-committee-papers-pdf-9256414285 , based on TA400
Diarrhoea	£182.00	NICE TA728 (£182) (2020). https://www.nice.org.uk/guidance/ta728/evidence/appraisal-consultation-committee-papers-pdf-9256414285 , based on TA400
Brain fog	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Dizziness	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Headache	£129.43	Non-consultant-led outpatient (£129; PSSRU 2024/25) + paracetamol 500 mg × 4 (eMIT 2024–25)
Flushing	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Itching	£133.93	Non-consultant-led outpatient (£129; PSSRU 2024/25) + hydrocortisone 1% cream 15 g (eMIT 2024–25)
Spots	£133.93	Non-consultant-led outpatient (£129; PSSRU 2024/25) + hydrocortisone 1% cream 15 g (eMIT 2024–25)
Gastrointestinal domain: outpatient consultation	£174.85	National costs collection for NHS 2023/24, Gastroenterology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 301).

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Resource use activity	Unit cost	Reference
		https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/
Skin domain: Dermatology outpatient consultation	£164.35	National costs collection for NHS 2023/24, 2023/24, Dermatology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 330)
Skin domain: Dermatologist nurse visit	£13.25	The cost of a GP practice nurse visit is estimated based on 15 minutes of nurse time (£53/per hour with qualification), the PSSRU (2024)-Section 9.3
Neurologic domain: outpatient consultation	£248.95	National costs collection for NHS 2023/24, Neurology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 400).
Accident & Emergency visit	£192.62	National costs collection for NHS 2023/24, A&E visit (Total Outpatient Attendance) - Average cost (Service code 180)
Hospitalisation	£3,804.93	National costs collection for NHS 2023/24, weighted average of non-elective long stay of Other Haematological or Splenic Disorders (SA08G-SA08J)
Daycase admission	£408.58	National costs collection for NHS 2023/24, weighted average of Day cases of Other Haematological or Splenic Disorders (SA08G-SA08J)
Anaphylaxis without complications	£1,554.71	Anaphylaxis without complications (assumed EpiPen tried but did not work), required ambulance (£250), A&E visit (£273), day case (£1031) from PSSRU& antihistamines (Cetirizine hydrochloride £0.71) from BNF
Anaphylaxis with complications	£6,486.00	Anaphylaxis with complications (assumed complications to be with brain (AA23C-G,£2991), heart (EB07A-E,£1334)& kidney (LE01A-B,LE02A-B,£857), A&E visit (£273), day case (£1031) from PSSRU)
EpiPen use	£60.69	Cost of EpiPen (300mcg) and ampoule of adrenaline (BNF 2025-Part VIIIA Category C)
Bone marrow biopsy	£787.01	National costs collection for NHS 2023/24, weighted average of total HRG: Diagnostic Bone Marrow Extraction (SA33Z)
ECG	£134.26	National costs collection for NHS 2023/24, RD15A - Simple Echocardiogram, 19 years and over
Haematology visit	£195.26	National costs collection for NHS 2023/24, Outpatient Attendances Data: 303- Clinical haematology, Consultant-Led
Biochemistry test: renal - Urea and electrolytes test (UE test)	£3.66	National costs collection for NHS 2023/24, DAPS101 - Clinical biochemistry-Urology service
Coagulation test	£5.89	National costs collection for NHS 2023/24, DAPS101- Haematology

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Resource use activity	Unit cost	Reference
Serum chemistry tests	£1.46	National costs collection for NHS 2023/24, DAPS04 - Clinical biochemistry
Phototherapy	£140.52	National costs collection for NHS 2023/24, JC47Z - Phototherapy or Photochemotherapy, 330-Dematology service
CT scan	£114.83	National costs collection for NHS 2023/24, Weighted average of RD20A (£102.7826813198982) and RD21A (£126.87247666303686)
Chest X-ray	£77.75	National costs collection for NHS 2023/24, RD50Z - Same day Diagnostic Imaging admission or attendance
Ultrasound scan	£64.60	National costs collection for NHS 2023/24, RD40Z - Ultrasound Scan with duration of less than 20 minutes, without Contrast
MRI scan	£161.65	National costs collection for NHS 2023/24, RD01A - Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
Full blood count	£2.98	National costs collection for NHS 2023/24, DAPS05-Haematology-999-Unknown
Bone densitometry	£77.75	National costs collection for NHS 2023/24, RD50Z - DEXA Scan

Abbreviations: A&E, accident and emergency; eMIT, electronic market information tool; GP, general practitioner; PSSRU, Personal Social Services Research Unit. A&E, accident and emergency; CT, computerised tomography; ECG, electrocardiogram.

Source: PSSRU (2024/2025)⁹⁸; British National Formulary¹¹⁷; eMIT database¹¹⁶ PSSRU unit cost drawn on NHS England's National Cost Collection 2023/2024, all costs inflated to 2024/2025.

Table 61 presents the average proportion of patients who experienced mild, moderate or severe symptoms in the PIONEER trial. Table 62 summarised the disease health state costs, demonstrating more HCRU costs required by treatment non-responders than treatment responders. The disease health state was defined by TSS (See section 3.3.2. for more details). The model assumed the delay for reduced resource usages at 12 cycles.

Table 61: Average proportion of patients experiencing any symptoms

Symptoms by severity	Mild	Moderate	Severe	Reference
Average % of patients experiencing any symptoms	██████	██████	██████	PIONEER TSS Health state summary

Abbreviations: TSS, total symptom score.

Table 62: Costs for disease health states by TSS

Resource use costs per cycle	Mild	Moderate	Severe
Non-responder			
Responder			

Abbreviations: TSS, total symptom score.

3.6.2.1 Costs associated with Smouldering and Advanced SM

The model assumed the monitoring costs for SSM and AdvSM the same as severe health state in non-responder as shown in Table 63. On transition into the SSM or AdvSM health states a once-off cost is applied to a proportion of patient who are eligible for haematopoietic stem cell transplantation (allo-HSCT) costs. Table 64 contains the once-off costs associated with progressing. The associate specialist cost is a monthly cost incurred over a period of 12 months. The full cost is assumed to occur at the point of transition into the health state. The cost for allo-HSCT was estimated from the NHS National Cost Collection database, combining codes SA38A, SA38B, SA39A, SA39B and SA40Z. The weighted average of the codes' associated costs was used to derive a single HSCT aggregate cost of £54,072.11. The model assumed ■■■ of either SSM or AdvSM patients may be eligible for allo-HSCT. Therefore, the expected costs for SSM and AdvSM patients were calculated based on the weighted average cost of allo-HSCT multiplied by 10% eligibility proportions, with the costs of £5,407.21.

Table 63: Total cost of disease management per health state

Monitoring costs	Unit cost	Reference
SSM		Assumption, same as severe health state
AdvSM		Assumption, same as severe health state

Abbreviations: AdvSM, advanced systemic mastocytosis; SSM, smouldering SM.

Table 64: One-off costs for advanced disease

Resources	Cost	Reference
Pre-HSCT cost	£1,727.90	NICE TA523
Allo-HSCT	£49,942.29	NHS National schedule of costs 2024/25
Associate specialist	£2,401.92	NICE TA523
Total	£54,072.11	Calculated

Abbreviations: HSCT, haemopoietic stem cell transplantation.

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 eMIT 2024 and PSSRU 2024/25.^{98,116} Resources used to manage each AE were identified from published sources, including NICE TA728 and the BNF.^{76,117} In the model, AE costs were calculated by multiplying the incidence of each AE (Table 49), by its associated unit costs. For simplicity, these costs are applied only in the first cycle of the model. Table 65 summarises the costs associated with AEs.

Table 65: AE-related costs

Adverse event	Cost	Reference
Headache	£0.43	eMIT 2024/25 (DDG325), assumed treatment with 4 tablets of paracetamol
Nausea	£182.00	NICE TA728(£182) (2020). ⁷⁶
Oedema peripheral	£46.99	Bumetanide drug used to treat, BNF price (£2.29) + 10 mins GP visit based on PSSRU (10*£4.47)
Periorbital oedema	£46.99	Assumed same as oedema peripheral
Fatigue	£91.68	NICE TA728 ⁷⁶
Flushing	£0.00	Assumption
Alopecia	£53.58	Assumed treated with Minoxidil BNF price (£8.88), + 10 mins GP visit based on PSSRU (10*£4.47)
Blood alkaline phosphatase increased	£90.03	Assumed same cost as alanine aminotransferase increased
Contusion	£47.78	Assumed that High compression bandages (£3.08 BNF) would be given by GP (10* £4.47)
Eyelid oedema	£46.99	Assumed same as oedema peripheral
Face oedema	£46.99	Assumed same as oedema peripheral
Aspartate aminotransferase increased	£182.13	Assumed same cost as alanine aminotransferase increased
Diarrhoea	£182.00	NICE TA728 ⁷⁶
Dizziness	£0.00	Assumption
Hair colour changes	£0.00	Assumption
Photosensitivity reaction	£0.00	Assumption
Alanine aminotransferase increased	£90.03	Assumed required a live function test (£13.33), and 10 mins GP consultant based on PSSRU (10*£4.47), and the cost of 30 minutes contact with a Band 6 nurse (£64/hour)

Adverse event	Cost	Reference
Blood lactate dehydrogenase increased	£90.03	Assumed same cost as alanine aminotransferase increased
Dry mouth	£49.62	BNF price for AS Saliva Orthant (£4.92) + 10 mins GP visit PSSRU (10*£4.47)
Muscle spasms	£46.10	Assumed to be treated with a muscle relaxant, Baclofen. BNF price (£1.40) + 10 mins GP Visit PSSRU (10*£4.47)

Abbreviations: A&E, accident and emergency; BNF, British National Formulary; eMIT, electronic market information tool; GP, general practitioner; PSSRU, Personal Social Services Research Unit; BNF, British National Formulary

Sources: PSSRU (2024/2025)⁹⁸; British National Formulary.¹¹⁷

3.6.4 End of life cost and resource use

Given the long-term nature of ISM in which mortality is not a primary driver of patient burden, and no mortality differences are assumed within ISM states, no end of life costs were included in the model.

3.7 Severity

In accordance with the NICE framework introduced in 2022, which allows severity modifiers to be applied to cost-effectiveness analysis (CEA) based on QALY shortfall.⁹¹ In line with the updated NICE process and methods, the absolute and proportional QALY shortfall were calculated in the CEM to assess the severity of ISM under current clinical management. Treatment for conditions with greater QALY shortfalls may be eligible for a higher WTP threshold in NICE's decision-making.^{91,139}

The equations used to calculate shortfall were as follows:

Absolute shortfall = Expected QALYs in general population – Expected QALYs with ISM

$$\text{Proportion shortfall} = \frac{\text{QALYs lost due to ISM}}{\text{Expected QALYs in general population.}}$$

Based on the model results, the discounted QALY outcome (at 3.5%) for SDT was 10.33, compared with 17.7 when undiscounted. Table 66 presents the QALY shortfall based on the base case result. Using the model's starting age of 40 years and a 73% female proportion, the absolute QALY shortfall was estimated at 8.35 (discounted) and 24.84 (undiscounted), corresponding to proportional shortfalls of 44.69% and 70.63%, respectively, via the validated QALY shortfall calculator.⁹¹

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Table 66: Quality-adjusted life-year shortfall

Parameter	Value	
Patient age	40	
% female	73	
Discount rate	3.5%	0%
QALYs without disease	18.68	35.17
QALYs with disease	10.33	
Absolute shortfall	8.35	24.84
Proportional shortfall	44.69%	70.63%
QALY weight	1	1.7

Abbreviation: QALY, quality-adjusted life-year

Under Section 6 of the NICE HTE Manual, severity weights are based on discounted QALY shortfall (reference case 3.5%).⁹¹ A weight of 1.0 (no modifier) applies only when both the proportional shortfall is less than 0.85 and the absolute shortfall is less than 12 QALYs; a weight of 1.2 applies if either proportional shortfall is in between 0.85 to 0.95 or absolute shortfall is in between 12 to 18 QALYs; a weight of 1.7 applies if either proportional shortfall is at least 0.95 or absolute shortfall is at least 18 QALYs. Although an undiscounted analysis might show an absolute shortfall is over 18 QALYs (which would imply a 1.7 weight), NICE committees base severity weighting on the discounted shortfalls; the undiscounted values are supplementary context only. Therefore, avapritinib must meet the standard £20,000–£30,000 per QALY cost-effectiveness range without a severity modifier if the discounted shortfalls fall below those thresholds.

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 or explored within CEM.

3.8.1 Uncertainty of clinical inputs

3.8.1.1 Lacking UK RWE data

Baseline characteristics were informed by the PIONEER trial, which primarily included patients from the United States and other international sites.^{54,80} However, as avapritinib has not yet received marketing authorisation for use in patients with Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

ISM in the UK, there is limited UK-specific RWE describing ISM patient characteristics, treatment patterns, or disease outcomes under avapritinib treatment.

As a result, uncertainty remains regarding the representativeness of the PIONEER population for UK clinical practice. To address this, sensitivity analyses were undertaken to assess the impact of these assumptions and alternative scenarios on model outcomes.

3.8.1.2 Generalisability of US population data

In the absence of UK RWE data, US RWE was incorporated into the CEA for avapritinib in the treatment of ISM in adults. The pivotal clinical evidence supporting avapritinib was derived primarily from an OLE cohort study conducted in the United States.⁹⁵ However, differences in clinical practice patterns, treatment pathways, and patient characteristics between the US and the UK introduce uncertainty regarding the generalisability of these data to the UK healthcare setting. To mitigate this limitation, three UK clinical experts in haematology and mastocytosis were consulted, and relevant published literature was used to validate the population generalisability and model assumptions and to ensure that the inputs were clinically plausible and reflective of UK practice.⁴⁴ Further details on the methodology used to integrate expert input are provided in Section 3.4.3.1.

3.8.1.3 Small patient size

The PIONEER clinical trials and available US RWE datasets include a limited number of patients, reflecting the rarity of ISM.^{54,80,95} This small sample size results in wide confidence intervals (CI) for clinical outcomes, contributing to parameter uncertainty within the CEM. To account for this uncertainty, a probabilistic sensitivity analysis (PSA) was conducted to quantify the impact of sampling variation and to assess its influence on the overall results.

3.8.1.4 Use of symptom severity measure

Currently, there is no universally accepted guideline for the standard measurement of ISM symptom severity in the UK clinical practice. The ISM-SAF (© Blueprint Medicines Corporation) is a PRO tool used in the PIONEER trial to assess and measure the symptoms of ISM through the TSS.^{53,54,56,80} However, the ISM-SAF (© Blueprint Medicines Corporation) is not routinely used in the UK clinical practice to

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evaluate symptom severity.⁵⁶ This limits the direct applicability of TSS-based efficacy outcomes to UK patients and introduces uncertainty regarding their interpretation in the NHS context. Where relevant, expert clinical input and validation were used to align symptom improvements observed in the trial with outcomes meaningful in the UK setting.⁴⁴

3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

The summary of variables applied to the CEM was presented in Appendix H.

A PSA was performed for the base case to account for joint uncertainty across parameters. This approach is consistent with the NICE reference case, which recommends probabilistic analysis as the preferred method for exploring parameter uncertainty.⁹¹ All parameters were included in the PSA, except for time horizon, discount rates and drug costs, as these are considered policy-driven or fixed inputs rather than stochastic variables.

Each parameter was assigned an appropriate probability distributions, and random values were drawn using Monte Carlo simulation techniques. The base case PSA was run for 1,000 iterations, which was sufficient to achieve stable and reproducible results.

A deterministic one-way sensitivity analysis (OWSA) was also performed to identify the key model drivers and assess the influence of individual parameters on the model outcomes. In OWSA, each parameter was varied systematically and independently varied over a plausible range determined by either the 95% CI (value $\pm 1.96 \times \text{SE}$), or, where unavailable, by $\pm 20\%$ of the base case value.

3.9.2 Assumptions

A summary of all model assumptions and justification is provided in Table 67.

Table 67: Model assumptions

Model input	Assumption	Rationale
Time horizon	Lifetime	ISM is a rare, chronic disease, a lifetime duration is sufficient to capture all benefits and costs of treatments for a chronic disease such as ISM, as per NICE reference case. ⁹¹

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Model input	Assumption	Rationale
Perspective	NHS in England and Wales, and PSS	Preference specified in the NICE reference case. ⁹¹
Cycle length	1 month (28 days)	The cycle length is 1 month to capture the costs and events associated with symptom severity changes based on the treatment response of ISM. Half-cycle correction was applied.
Efficacy	- Treatment efficacy was measured by TSS changes from the PIONEER trial. (See section 3.3.3 for symptom definition derived by TSS); Table 42 and Table 43 presents the TSS changes in 252 weeks (64 cycles). - Due to the limited trial period, the US RWE analysis was incorporated in the absence of UK population data for the base case. - The expected ToT is around [REDACTED] years for an avapritinib responder was extrapolated using US RWE analysis in the absence of UK population data for the base case. - Treatment waning to SDT was assumed to start after [REDACTED] cycles of avapritinib discontinuation using clinical experts' options. [REDACTED] avapritinib discontinuation rate was directly derived from the PIONEER trial.¹⁰⁴ - Patients who discontinued from avapritinib and switched to SDT were assumed to revert to baseline	Economic analysis uses the PIONEER trial data (February 2025 DCO) and incorporates with US RWE data for DoT analyses ^{80,95}
Comparators	A basket of SDT drugs including H1-blockers, H2-blockers, omeprazole, montelukast, prednisolone, nalcrom, and omalizumab, consistent with the NICE scope.⁹³ TKIs (e.g. midostaurin, imatinib,	Patients with uncontrolled severe ISM may be treated with TKIs. However, as per UK clinical experts' opinions, TKIs are not commonly used in the current NHS practice. ⁴⁴ Therefore, scenario analysis explored the uncertainty when excluding TKIs in the treatment.

Model input	Assumption	Rationale
	dasatinib) were also included in the base case. Exclusion of using TKIs was tested in the scenario analysis.	
Utility	Utility values are assumed to differ by health state and symptom severity, but not by treatment arm	- Utility of ISM health state by TSS changes in PIONEER trial was selected because disease symptom severity (mild, moderate and severe) was the strongest predictor of patient utility.^{54,80} - Utility for SSM was derived from the Dutch Expert advisory board, and utility value for AdvSM was sourced from TA1012, estimated from the PATHFINDER trial.^{11,92,97} - HRQoL results from PIONEER showed lower utility at baseline for those SDT, as it is assumed they have already experienced disease progression. ISM utility values were validated by three UK clinical experts.⁴⁴
Costs	- The drug cost of treatment is assumed to differ by treatment arms, not by health state and symptom severity, aligning with the administration route indicated in the SmPC.¹ - Avapritinib is assumed to be used along with SDT. - The proportion of using SDT is assumed to be different for avapritinib plus SDT versus SDT alone (see Table 39).	Discussion with three UK clinical experts, no additional costs or healthcare resource use costs are expected for the treatment with avapritinib.⁴⁴ The proportion of SDT used with and without avapritinib are validated with three UK clinical experts.⁴⁴

Abbreviations: DCO, data cut-off; ISM, indolent systemic mastocytosis; SSM, smouldering systemic mastocytosis; AdvSM, advanced systemic mastocytosis; PSS, personal social service; RWE, real-world evidence; TSS total symptom score; HRQoL, health-related quality of life; DoT, duration on treatment; QALY, quality-adjusted life-year; SDT, symptom-directed therapy; TKIs, tyrosine kinase inhibitors.

3.10 Base case results

3.10.1 Base case incremental cost-effectiveness analysis results

The base case CEA compared avapritinib with SDT from the NHS and Personal Social Services perspective. The analysis incorporated the PAS confidential discount

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for avapritinib ([REDACTED] reduction from the list price). The results are presented in Table 68.

Table 68: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Avapritinib (list price)	[REDACTED]	19.23	10.95	[REDACTED]	0.06	0.62	[REDACTED]
Avapritinib (PAS price)	[REDACTED]			[REDACTED]			[REDACTED]
SDT	£530,089	19.18	10.33				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life-years; SDT, symptom-directed therapy.

As shown in Table 69 and Table 70, treatment with avapritinib was associated with substantial health benefits compared with SDT, providing an incremental 0.06 LYs and 0.62 QALYs per patient. The improvement in QALYs was mainly attributable to prolonged time spent in the mild disease health state and a reduced duration in the severe disease state. These findings are consistent with the treatment effect of avapritinib, which demonstrated a $\geq 30\%$ reduction in TSS among responding patients, reflecting meaningful symptom improvement and enhanced quality of life.

Table 69: Discounted life-year by health state breakdown

	Avapritinib arm	SDT arm	Incremental life-year
Total life-years	19.23	19.18	0.06
Life-years for Mild	3.61	1.12	2.49
Life-years for Moderate	4.79	5.39	-0.60
Life-years for Severe	9.31	10.87	-1.57
Life-years for SSM	0.46	0.54	-0.08
Life-years for ASM	1.06	1.25	-0.19

Abbreviations: SDT, symptom-directed therapy; SSM, smouldering systemic mastocytosis; AdvSM, advanced systemic mastocytosis.

Table 70: Discounted QALYs by health state breakdown

	Avapritinib arm	SDT arm	Incremental QALYs
Total QALYs	10.95	10.33	0.62
QALYs for Mild	2.74	0.83	1.91
QALYs for Moderate	3.05	3.45	-0.40
QALYs for Severe	4.42	5.17	-0.75
QALYs for SSM	0.23	0.27	-0.04
QALYs for ASM	0.52	0.62	-0.10
Disutility AE	0.00	0.00	0.00

Abbreviations: QALYs, quality-adjusted life-years; SDT, symptom-directed therapy; SSM, smouldering systemic mastocytosis; AdvSM, advanced systemic mastocytosis; AE, adverse event

3.10.1.1 Avapritinib at the list price

As shown in Table 71, the discounted cost breakdown at the list price that drug acquisition costs of avapritinib account for the majority of the incremental cost impact. Specifically, avapritinib drug costs contribute [REDACTED] of the total incremental costs [REDACTED], offset only minimally by reductions in SDT and monitoring costs. Correspondingly, Table 68 demonstrates that these health gains and incremental costs resulted in an ICER of [REDACTED] per QALY gained for avapritinib versus SDT at the list price.

However, after applying the [REDACTED] confidential PAS discount (final avapritinib price of [REDACTED] per pack), the ICER for avapritinib versus SDT is expected to fall within the range (£20,000 to £30,000) considered cost-effective by NICE.

This overall cost pattern is further supported by Table 72, which presents the discounted cost breakdown by health state at list price. The majority of total and incremental costs arise during time spent in the ISM mild health state, reflecting both the long duration of time patients remain in this state under avapritinib treatment and continued drug acquisition costs during this period. Costs in more severe ISM states, SSM, and AdvSM contribute relatively little to overall incremental cost differences, consistent with the clinical expectation that avapritinib maintains patients in earlier, less severe health states for longer.

Table 71: Discounted cost breakdown (list price)

	Avapritinib arm	SDT arm	Incremental
Total Costs	██████████	£530,089	██████████
Drug acquisition costs	██████████	£67,980	██████████
<i>Avapritinib</i>	██████████	£0	██████████
<i>SDT</i>	██████████	£67,980	██████████
Drug administration costs	██████████	£33	██████████
Resource use and monitoring costs	██████████	£460,799	██████████
Adverse events costs	██████████	£38	██████████
Advanced disease costs	██████████	£1,239	██████████

Abbreviations: SDT, symptom-directed therapy; SSM, smouldering systemic mastocytosis; AdvSM, advanced systemic mastocytosis.

Table 72: Discounted cost breakdown by health states (list price)

By health state	Avapritinib	SDT	Incremental
ISM Mild	XXXXXXXXXX	£30,027	XXXXXXXXXX
ISM Moderate	XXXXXXXXXX	£147,299	XXXXXXXXXX
ISM Severe	XXXXXXXXXX	£305,994	XXXXXXXXXX
SSM	XXXXXXXXXX	£14,163	XXXXXXXXXX
AdvSM	XXXXXXXXXX	£32,606	XXXXXXXXXX
Total	XXXXXXXXXXXX	£530,089	XXXXXXXXXXXX

Abbreviations: AdvSM, advanced systemic mastocytosis; ISM, indolent SM; SSM, smouldering SM; SDT, symptom-directed therapy.

3.10.1.2 Avapritinib at the PAS price discount

Total discounted costs were estimated to be ██████████ for avapritinib and £530,089 for SDT, resulting in incremental costs of ██████████ per patient (See Table 73). Given the incremental QALY gain, avapritinib is therefore dominant compared with SDT, being both less costly and more effective when the PAS discount is applied.

The health-state distribution of costs demonstrates that although avapritinib incurs higher costs in the mild ISM health state due to improved symptom control and increased time spent in this less severe state, this is offset by substantial cost reductions in more severe health states, particularly ISM Severe and Moderate. These reductions reflect fewer symptoms, lower HCRU, and delayed progression associated with treatment. Overall, the total discounted incremental cost difference ██████████ aligns with the model's conclusion that avapritinib is a cost-saving intervention relative to SDT when PAS is applied.

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Table 73: Discounted cost breakdown (PAS discount applied)

By item	Avapritinib arm	SDT arm	Incremental
Total Costs		£530,089	
Drug acquisition costs		£67,980	
<i>Avapritinib</i>		£0	
<i>SDT</i>		£67,980	
Drug administration costs		£33	
Resource use and monitoring costs		£460,799	
Adverse events costs		£38	
Advanced disease costs		£1,239	

Abbreviations: SDT, symptom-directed therapy; Note: advanced disease costs include the costs of SSM (smouldering systemic mastocytosis) and AdvSM (advanced systemic mastocytosis).

Table 74: Discounted cost breakdown by health states (PAS discount applied)

By health state	Avapritinib	SDT	Incremental
ISM Mild		£30,027	
ISM Moderate		£147,299	
ISM Severe		£305,994	
SSM		£14,163	
AdvSM		£32,606	
Total		£530,089	

Abbreviations: AdvSM, advanced systemic mastocytosis; ISM, indolent SM; SSM, smouldering SM; SDT, symptom-directed therapy.

3.10.1.3 Net health benefit

To support interpretation of cost-effectiveness outcomes, net health benefit (NHB) and net monetary benefit (NMB) were calculated for avapritinib versus SDT at WTP thresholds of £20,000 and £30,000 per QALY gained. Results are presented in Table 75, separately for avapritinib at list price and avapritinib with the PAS discount applied.

At the list price, avapritinib generated negative incremental NHB and NMB values at both WTP thresholds, indicating it is not cost-effective compared with SDT.

When the PAS discount (confidential) is applied, avapritinib demonstrates positive NHB and NMB values at both thresholds, indicating that it is cost-effective and dominant versus SDT, being both less costly and more effective.

Table 75: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental NHB at £20,000	Incremental NHB at £30,000	Incremental NMB at £20,000	Incremental NMB at £30,000
Avapritinib (list price)		10.95		0.62				
Avapritinib (PAS price)		10.95						
SDT	£530,089	10.33	-	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHB, net health benefit; QALYs, quality-adjusted life-years; SDT, symptom-directed therapy.

Appendix H presents clinical outcomes from CEA and disaggregated results of the base case incremental CEA.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A PSA was conducted to quantify the combined uncertainty in model inputs and its impact on the cost-effectiveness results. Probability distributions were assigned to key parameters, and 1,000 Monte Carlo simulations were performed to jointly sample from these distributions. This approach allows estimation of the variability in both costs and outcomes due to parameter uncertainty, consistent with NICE reference case methodology.⁹¹

To ensure transparency in reporting, the PSA results for avapritinib versus a basket of SDT are presented separately for avapritinib at the list price and at the PAS price, including the corresponding cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC).

3.11.1.1 Avapritinib in the list price

For avapritinib versus a basket of SDT, the mean PSA results are summarised in Table 76. At the list price, the CEP (Figure 19) shows that the majority of simulations fall within the northeast quadrant, indicating that avapritinib is consistently more

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costly and more effective than SDT. The distribution of points demonstrates a linear relationship between incremental costs and incremental QALYs, with limited dispersion, reflecting moderate parameter uncertainty and good internal model stability.

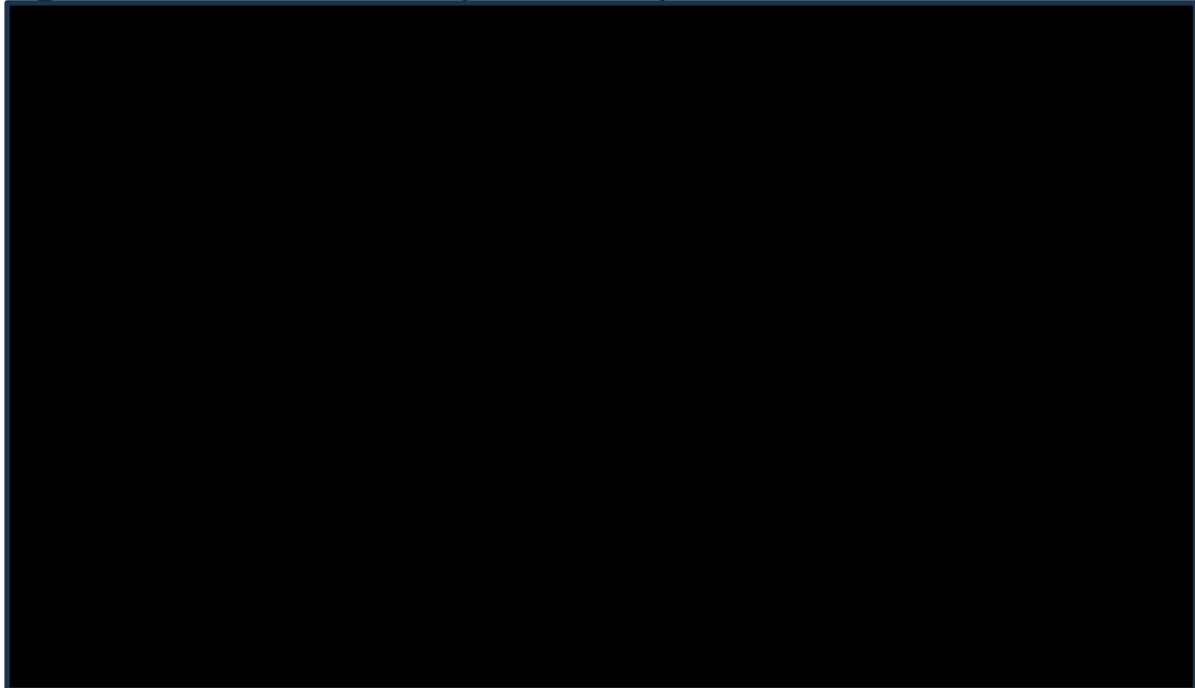
The CEAC (Figure 20) demonstrates that the probability of avapritinib being cost-effective at the standard NICE WTP threshold (£20,000–£30,000 per QALY) is close to 0%. This PSA outcome reflects the high incremental cost associated with avapritinib and the resulting base case ICER of £[REDACTED] per QALY gained, and a PSA mean ICER of £[REDACTED] per QALY, both of which is well above the conventional threshold range.

Table 76: Probabilistic sensitivity analysis for avapritinib versus SDT

Analysis	Total cost (Avapritinib)	Total cost (SDT)	Incremental cost (£)	Total QALYs (Avapritinib)	Total QALYs (SDT)	Incremental QALYs	ICER (£/QALY)
Base case (deterministic)	[REDACTED]	£530,089	[REDACTED]	10.95	10.33	0.62	[REDACTED]
PSA mean	[REDACTED]	£530,230	[REDACTED]	10.83	10.22	0.61	[REDACTED]
95% CI (lower)	[REDACTED]	£450,090	[REDACTED]	10.12	9.55	0.41	[REDACTED]
95% CI (upper)	[REDACTED]	£620,857	[REDACTED]	11.53	10.93	0.86	[REDACTED]

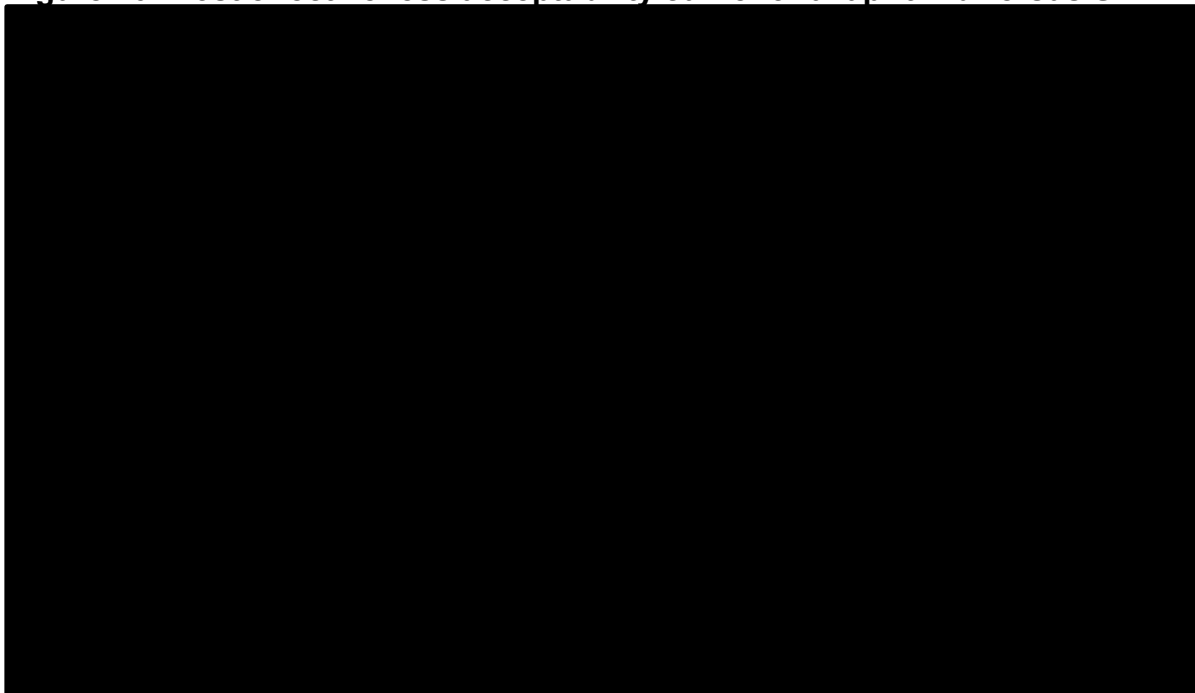
Abbreviations: QALYs, quality-adjusted life-years; SDT, symptom-directed therapy; 95% CI, 95% confidence interval; PSA, probabilistic sensitivity analysis; ICER, incremental cost-effectiveness ratio

Figure 19: Cost effectiveness plane for avapritinib versus SDT



Abbreviations: QALY, quality-adjusted life-year; SDT, symptom-directed therapy.

Figure 20: Cost effectiveness acceptability curve for avapritinib versus SDT



Abbreviations: QALY, quality-adjusted life-year; SDT, symptom-directed therapy.

3.11.1.2 Avapritinib with PAS discount

After applying the PAS discount ([REDACTED]; confidential), the incremental costs of avapritinib decrease substantially, resulting in a significant improvement in its cost-effectiveness profile.

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The CEP () shows that the majority of simulations fall within the south-east (SE) quadrant, where incremental QALYs are positive and incremental costs are negative. This indicates that avapritinib is less costly and more effective than SDT in most model iterations, which means avapritinib is dominant when the PAS price is applied. The tight distribution of points indicates limited variability and a high degree of confidence that avapritinib remains economically dominant across plausible parameter ranges. Only a small proportion of iterations fall above the x-axis, suggesting few scenarios in which avapritinib is more costly than SDT.

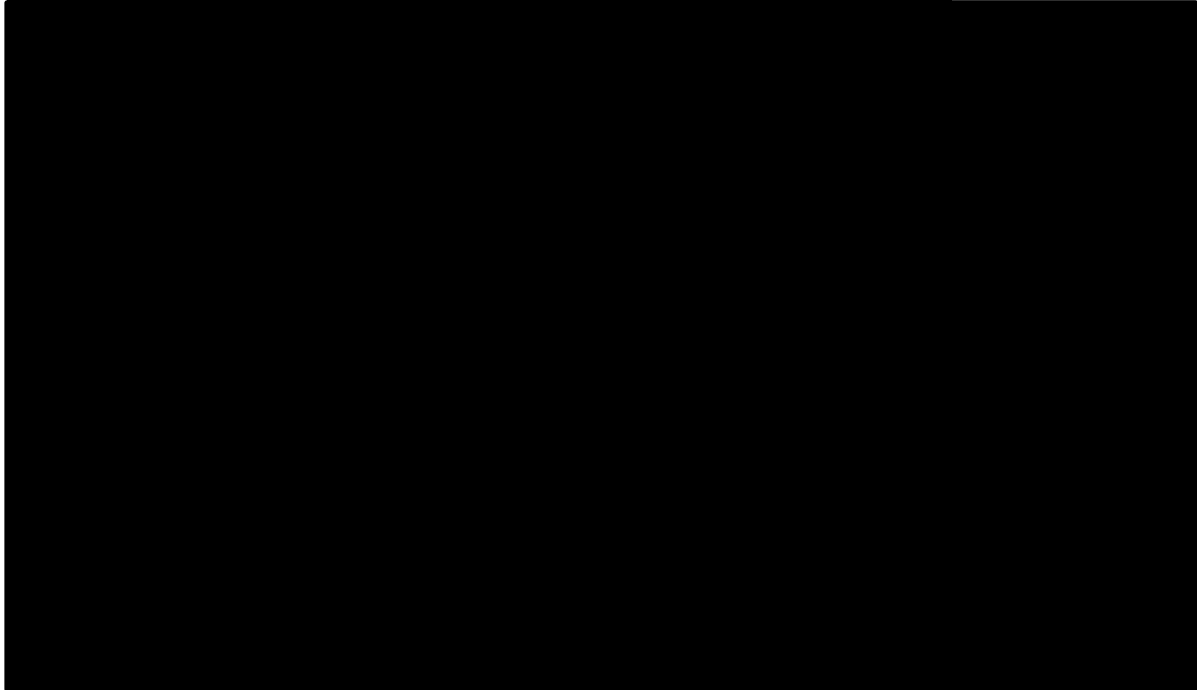
The CEAC () illustrates the probability of avapritinib being cost-effective at different WTP thresholds. At a threshold of £0 per QALY, avapritinib already shows a probability exceeding , demonstrating that it is cost-saving in most simulations even when no value is assigned to health gain. This probability increases steadily with higher thresholds, reaching at £20,000 per QALY and approaching at £30,000 per QALY, whereas the probability for SDT declines toward zero. These results confirm the dominance and robust cost-effectiveness of avapritinib under the PAS discount scenario.

Table 77: Probabilistic sensitivity analysis for avapritinib versus SDT (PAS discounted)

Analysis	Total cost (Avapritinib)	Total cost (SDT)	Incremental cost (£)	Total QALYs (Avapritinib)	Total QALYs (SDT)	Incremental QALYs	ICER (£/QALY)
Base case (deterministic)		£530,089		10.95	10.33	0.62	
PSA mean		£532,691		10.82	10.22	0.60	
95% CI (lower)		£453,886		10.09	9.54	0.41	
95% CI (upper)		£614,264		11.49	10.88	0.83	

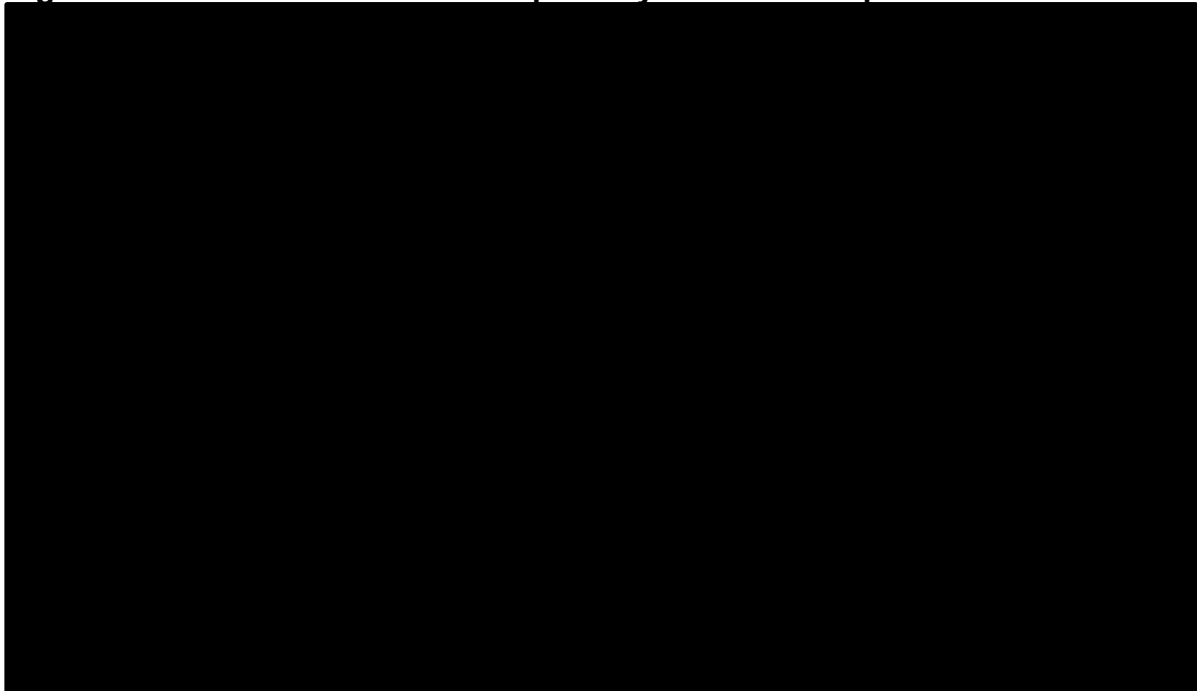
Abbreviations: QALYs, quality-adjusted life-years; SDT, symptom-directed therapy; 95% CI, 95% confidence interval; PSA, probabilistic sensitivity analysis; ICER, incremental cost-effectiveness ratio

Figure 21: Cost effectiveness plane for avapritinib versus SDT



Abbreviations: QALY, quality-adjusted life-year; SDT, symptom-directed therapy.

Figure 22: Cost effectiveness acceptability curve for avapritinib versus SDT



Abbreviations: QALY, quality-adjusted life-year; SDT, symptom-directed therapy.

The PSA results demonstrate some variability in total costs and QALYs across simulations, reflecting underlying parameter uncertainty, but the incremental results remain stable. The PSA mean values are closely aligned with deterministic base

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case estimates, confirming that the model is internally consistent and not overly sensitive to random variation.

At the list price, avapritinib remains associated with higher costs and some QALY gains, resulting in ICERs well above NICE's accepted thresholds. When the PAS discount is applied, avapritinib becomes dominant versus SDT in most simulations, providing greater health benefit at lower cost, with approximately 90% probability of being cost-effective across all relevant WTP thresholds.

3.11.2 One-way sensitivity analysis

An OWSA was conducted to assess the impact of parameter uncertainty on the model base case result. Each parameter was varied individually across a plausible range while holding all other parameters constant. The ranges were defined based on 95% CI, or, where these were unavailable, a variation of $\pm 20\%$ around the base case value was applied.

3.11.2.1 *Avapritinib in the list price*

The results for the ten most influential parameters are summarised in Table 78 and illustrated in Figure 23.

The model was found to be most sensitive to changes in utility values, particularly for the aggressive systemic mastocytosis (ASM), age-adjusted 40 years, severe and mild health states. Other influential parameters included anaphylaxis with complications, utilities for SSM health state and drug acquisition costs for midostaurin.

Overall, the variation in incremental cost-utility ratio (ICUR) values across all parameters was modest, suggesting that the model is robust and that no single parameter exerts an excessive influence on cost-effectiveness results.

Table 78: Top 10 in ranking in OWSA

Parameter	Lower	Upper	Difference ΔICUR
Utilities ASM			
40 utility			
Utilities Severe			
Utilities Mild			
Anaphylaxis with complications			
Utilities SSM			
Midostaurin: cost per package			
Adjust utility for response			
From Severe to AdvSM			
Utilities Moderate			

Abbreviation: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ICUR, incremental cost-utility analysis; OWSA, one-way probabilistic sensitivity analysis; SSM, smouldering systemic mastocytosis; ToT, time-on-treatment.

The tornado diagram (Figure 23) illustrates that the ICER is most affected by uncertainty in utility estimates and treatment duration, while cost and transition parameters have a comparatively smaller effect. Despite this, none of the parameter variations shifted the ICER close to the NICE WTP thresholds (£20,000-£30,000 per QALY), reinforcing the stability of the base case findings.

Figure 23: Deterministic sensitivity analysis outputs

Abbreviation: ICUR, incremental cost-utility analysis; ToT, time-on-treatment; SSM, smouldering systemic mastocytosis; AdvSM, advanced systemic mastocytosis.

3.11.2.2 Avapritinib with PAS discount

Following the application of the PAS discount (), the cost-effectiveness results demonstrate minimal sensitivity to parameter variation, indicating that the model outcomes are robust to plausible changes in key assumptions.

The results for the ten most influential parameters are summarised in Table 79 and illustrated in Figure 24. Under the PAS price, the model was found to be most sensitive to assumptions relating to anaphylaxis with complications, average treatment duration (time-on-treatment), and drug acquisition costs for midostaurin. Other cost parameters, such as outpatient consultations and diagnostic procedures showed comparatively smaller impacts on the ICER.

Table 79: Top 10 in ranking in OWSA after PAS discount

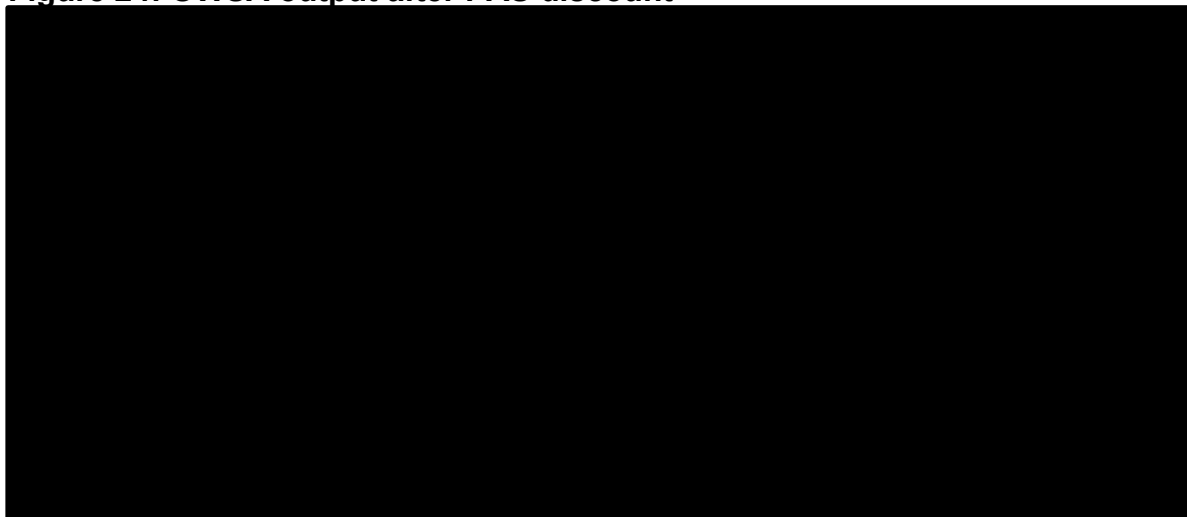
Parameter	Lower	Upper	Difference Δ ICUR
Anaphylaxis with complications			
Average ToT			
Midostaurin: cost per package			
Anaphylaxis without complications			
Neurologic domain: outpatient consultation: unit cost			
Bone marrow biopsy			
Neurologic domain: outpatient consultation			
Bone marrow biopsy: unit cost			
Gastrointestinal domain: outpatient consultation			
Skin domain: Dermatology outpatient consultation: unit cost			

Abbreviation: ICUR, incremental cost-utility analysis; OWSA, one-way probabilistic sensitivity analysis; PAS, patient access scheme; ToT, time-on-treatment.

As shown in Figure 24, the OWSA confirms that avapritinib remains dominant compared with SDT across all parameter ranges evaluated, which is less costly and more effective under the PAS discount scenario. The limited variation in ICER values across parameters demonstrates the stability and robustness of the model. These findings reinforce the conclusion that the PAS discount is the primary driver of cost-effectiveness for avapritinib, ensuring consistent dominance over SDT even when key model parameters are varied within plausible limits.

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Figure 24: OWSA output after PAS discount



Abbreviation: ICUR, incremental cost-utility analysis; OWSA, one-way probabilistic sensitivity analysis; PAS, patient access scheme; SDT, symptom-directed therapy; ToT, time-on-treatment.

3.11.3 Scenario analysis

In accordance with the NICE reference case, a series of scenario analyses were undertaken to explore the impact of alternative structural and parameter assumptions on model outcomes. These analyses tested both optimistic and pessimistic assumptions to assess the robustness of the base case findings and identify potential sources of structural uncertainty in the cost-effectiveness results.⁹³

3.11.3.1 *Avapritinib in the list price*

Table 80 summarises the alternative scenarios evaluated at the list price of avapritinib. The tested scenarios included variations in model assumptions related to treatment duration, starting age, utility adjustments, resource use reduction, mortality risk, and dose escalation.

Across all scenarios, avapritinib remained cost-effective or dominant, with ICERs ranging from £ [REDACTED] per QALY. The lowest ICERs were observed under scenarios assuming 50% resource use reduction, higher mortality risk (Kibsgaard et al., 2020)²⁰ or assumed a zero number of patients in the health state distribution. Conversely, assuming a 5-year or 10-year time horizon, or applying SDT during the maintenance period, results in higher ICERs, indicating that avapritinib provides better economic value when used over the long term.

These results confirm that even under conservative assumptions, the PAS discount substantially improves the economic value of avapritinib, positioning it within or near NICE's cost-effectiveness thresholds across most plausible scenarios.

Overall, the results demonstrate that at the list price, avapritinib remains above NICE's accepted cost-effectiveness thresholds, even under optimistic assumptions.

Table 80: Scenarios tested within the cost-effectiveness analysis

Scenario	Incremental costs	Incremental QALYs	ICER
Suggested base case		0.621	
Time horizon 5-years		0.393	
Time horizon 10-years		0.588	
Time horizon 20-years		0.598	
Starting age: 51		0.622	
Starting age: 36		0.612	
Minimum number of patients (health state distribution) - 0		0.648	
Minimum number of patients (health state distribution) - 20		0.609	
ToT 1 years		0.417	
ToT 2 years		0.759	
ToT 3 years		0.884	
Wane after 1 months		0.623	
SSM utility 0.5		0.615	
No utility adjustment for treatment		0.593	
0% SDT reduction		0.621	
50% Resource use reduction		0.621	
25% Resource use reduction		0.621	
0% Resource use reduction		0.621	
Mortality HR 1.53 (Mukherjee et al. 2024)		0.630	
Mortality differentiated HR 1.53/2.06/2.59 (Kibsgaard et al. 2020)		0.654	
Midostaurin usage - 5%		0.621	
TKI usage 0%		0.621	
SDT maintain post-trial effect		0.472	

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SDT, symptom-directed therapy; SSM, smouldering systemic mastocytosis; TKI, tyrosine kinase inhibitors; ToT, time-on-treatment.

As shown in Table 81, after applying the [REDACTED] PAS discount, the same structural and parameter scenarios were tested to evaluate the robustness of cost-effectiveness results under the reduced price.

Across all scenarios, avapritinib remained cost-effective or dominant. The lowest ICERs were observed under scenarios assuming a resource use reduction of 50%, and 25%, or shorter treatment duration (5 years). Conversely, in the scenario of 0% TKI usage, 5% midostaurin usage or no resource use reduction produced the three highest ICERs, driven by decreased SDT treatment costs.

These results confirm that even under conservative assumptions, the PAS discount substantially improves the economic value of avapritinib, positioning it within or near NICE's cost-effectiveness thresholds across most plausible scenarios.

Table 81: Scenarios tested within the cost-effectiveness analysis (PAS price)

Scenario	Incremental costs	Incremental QALYs	ICER
Suggested base case		0.621	
Time horizon 5-years		0.393	
Time horizon 10-years		0.588	
Time horizon 20-years		0.598	
Starting age: 51		0.622	
Starting age: 36		0.612	
Minimum number of patients (health state distribution) - 0		0.648	
Minimum number of patients (health state distribution) - 20		0.609	
ToT 1 years		0.417	
ToT 2 years		0.759	
ToT 3 years		0.884	
Wane after 1 months		0.623	
SSM utility 0.5		0.615	
No utility adjustment for treatment		0.593	
0% SDT reduction		0.621	
50% Resource use reduction		0.621	
25% Resource use reduction		0.621	
0% Resource use reduction		0.621	
Mortality HR 1.53 (Mukherjee et al. 2024)		0.630	
Mortality differentiated HR 1.53/2.06/2.59 (Kibsgaard et al. 2020)		0.654	
Midostaurin usage - 5%		0.621	
TKI usage 0%		0.621	
SDT maintain post-trial effect		0.472	

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year; SDT, symptom-directed therapy; TKI, tyrosine kinase inhibitors; SSM, smouldering systemic mastocytosis

Scenario analyses confirmed that the model is structurally robust, with results generally stable across a wide range of alternative assumptions. The key drivers of cost-effectiveness were treatment duration, dose escalation, and stopping rules, consistent with clinical expectations.

At the list price, avapritinib remains above NICE's cost-effectiveness thresholds across all plausible scenarios. However, when the PAS discount is applied,

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avapritinib becomes dominant or highly cost-effective in nearly all tested conditions, reinforcing the reliability and consistency of the base case findings.

3.12 Subgroup analysis

Subgroup patients were excluded from this analysis (See Section 3.3.1). Therefore, no subgroup analyses were performed.

3.13 Benefits not captured in the QALY calculation

Avapritinib is administered once daily, which may reduce treatment burden compared with the basket of SDT regimens that often involve multiple drugs or complex dosing schedules. Although this convenience could improve patient adherence and satisfaction, there is insufficient quantitative evidence to estimate its impact on utility, and KOLs did not consider it plausible to provide a reliable adjustment.⁴⁴

In addition, by reducing symptom severity and improving functioning, avapritinib may confer indirect benefits not captured under the NHS and PSS perspective, including improved patient productivity and reduced caregiver burden. These potential gains are not incorporated in the CEM, as they fall outside the scope of the reference case.⁹¹

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

The CEM was developed in accordance with NICE's reference case and follows NICE's preferred methodological standards for health technology evaluations. The model adopted an NHS and PSS perspective and applied a lifetime time horizon to capture all relevant costs and QALY gains associated with avapritinib and comparator treatments.⁹¹

Comprehensive quality-control procedures were undertaken to ensure the accuracy and integrity of both the model simulation and its conceptual implementation. These procedures included verification of all input data with original sources; internal programme validation, comprising checks of the model calculations, logical consistency, and data references; review of model interface and Visual Basic for

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Application (VBA) code to confirm correct operation and data flow; and Cross-checking of model outputs against expected clinical and economic patterns.

To ensure face validity, the model structure, key assumptions, and input parameters were reviewed and validated by three UK clinical experts and incorporated with Dutch consultant opinions with expertise in the management of systemic mastocytosis. Their input confirmed that the model appropriately reflects the clinical pathway, disease progression, and treatment patterns relevant to the UK healthcare setting.⁴⁴

B3.16 Interpretation and conclusions of economic evidence

ISM is a rare clonal MC disease driven by the *KIT D816V* mutation in mast cells, which leading broad heterogeneous symptoms (skin, GI, anaphylaxis and osteoporosis) contribute to considerable disease burden including poor clinical outcomes and reduced HRQoL.¹⁵⁻¹⁷ Currently, there is no NICE-recommended targeted therapy for the treatment of ISM driven by *KIT D816V* mutations. In the UK clinical practice, SDT comprises a basket of symptomatic therapies targeting individual manifestations of the disease (see Table 39). Clinical evidence from the PIONEER study has demonstrated that avapritinib provides superior clinical outcomes compared with SDT alone across all ISM patient subgroups.^{54,80}

A *de novo* economic model was developed to reflect the natural history of ISM, as no previous economic evaluations for this indication were identified in published literature. The model structure was validated by three UK consultant haematologists, who confirmed its clinical plausibility and relevance to NHS practice.⁴⁴

Base case results showed that avapritinib at PAS discount price (██████████) is dominant versus SDT at a WTP threshold of £20,000 per QALY gained, from the NHS and PSS perspective. Treatment with avapritinib was associated with substantial QALY gains and clinically meaningful symptom improvements.

Comprehensive scenario analyses confirmed the stability of results under a wide range of alternative assumptions. At the list price, avapritinib was associated with higher costs and greater QALYs compared with SDT, resulting in an ICER of £██████████ per QALY gained when compared with SDT (including TKIs) and Company evidence submission template for avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

£[REDACTED] per QALY gained versus SDT without TKIs in scenario analyses. Following application of the [REDACTED] confidential PAS discount, avapritinib became dominant versus SDT, providing greater health benefits at lower total costs for moderate to severe adult ISM patients, from both NHS and PSS perspectives.

In line with NICE guidance, both structural and parameter uncertainties were explored through PSA, OWSA, and scenario analyses.⁹¹ The results demonstrated consistent findings across all analyses, reinforcing the robustness and internal validity of the base case model.

Strengths

- The economic analysis is underpinned by data from PIONEER, a robust, randomised, controlled trial with low risk of bias and a study population representative of expected ISM patients in England and Wales.
- Uncertainty was thoroughly assessed through multiple sensitivity and scenario analyses, with findings confirming the stability and credibility of model assumptions.
- The model structure was clinically validated by UK consultant haematologists to ensure face validity and alignment with NHS treatment pathways.

Limitations

- The primary limitation relates to the absence of UK-specific RWE describing long-term treatment patterns and outcomes with avapritinib. Consequently, the model relied on US-based RWE for extrapolation beyond the trial period, introducing inherent uncertainty.
- Given the rarity of ISM, available data are limited, and some assumptions were necessary to populate the model. To mitigate these limitations, expert clinical validation was obtained from UK haematologists to ensure the credibility and plausibility of key model assumptions.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Summary of Information for Patients (SIP)

November 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6578 Avapritinib SIP	Final	No	24 Nov 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic: Avapritinib 25 mg tablet for oral daily administration.
Brand name: Ayvakyt®

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

Avapritinib is anticipated, as per its marketing authorisation, to be used to treat adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.¹ ISM is the most common and milder form of systemic mastocytosis (SM), typified by *KIT D816V* gene mutation in mast cells in the majority (95%) of adult cases. This heterogeneous condition presents with considerable disease burden on account of persistent, debilitating symptoms across multiple body systems (such as skin, gut, and neurological function), which results in poor quality of life in people with ISM.²⁻⁴ Notably, ISM is clinically different from advanced systemic mastocytosis (AdvSM; including aggressive subtypes like mast cell leukaemia) because ISM patients do not present with organ damage due to the infiltration of mast cells (C-findings), and do not typically show signs of high mast cell burden (B-findings).⁵

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 through the international recognition procedure (IRP) route was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and is pending approval (see Document B1 for further details on anticipated dates for approval).¹ Avapritinib received EU marketing authorisation in December 2023 as the first and only treatment for adult patients with ISM with moderate-to-severe symptoms inadequately controlled on symptomatic treatment.⁶

In May 2023, avapritinib was approved by the Food and Drug Administration (FDA) for the treatment of adult patients with ISM.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 (UKmasto). The UK Mastocytosis Support Group is a leading patient advocacy group in England (Wales and Northern Ireland) supporting research into ISM, and care of people living with ISM. The Perceptions Realities and Insights on Systemic Mastocytosis (PRISM) study is Blueprint Medicines Corporation sponsored with involvement by UKmasto chair Jess Hobart. Blueprint Medicines Corporation is also providing grant support for a nationwide SM registry in US/UK with UKmasto co-leading the UK arm of the registry.

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.

ISM is a rare and complex blood disorder.⁸ This condition involves the excessive growth and activity of immune cells known as mast cells. These cells accumulate in various tissues throughout the body, including the bone marrow, spleen, liver, lymph nodes and the digestive system. ISM is the most common form of systemic mastocytosis, accounting for approximately 95% of adult cases.^{9,10} While detailed statistics specifically for England are limited, clinical and patient experts estimate that around 1 in every 10,000 people in the UK may be affected by ISM.^{11,12}

The condition causes a broad and unpredictable range of symptoms, driven by the unchecked release of inflammatory chemicals (mediators) from the mast cells.^{8,13} In about 95% of ISM cases, this uncontrolled growth and activation are driven by a change in the *KIT* gene, known as the *KIT D816V* mutation.^{10,14,15} Patients with moderate-to-severe ISM often experience a persistent and debilitating array of symptoms.^{2,16} According to a European survey in 237 ISM patients across seven European countries including the UK, the most common issues reported in this group include skin-related issues (17%, including hives, itching, spots on the skin, and flushing) and gastrointestinal problems (20%, including stomach bloating, nausea, heartburn, abdominal pain, and changes in bowel movements).¹⁷ The Mast Cell Connect Registry, which surveyed 88 ISM patients in the US and Canada with moderate-to-severe symptoms, reported severe fatigue (72%) and abdominal pain (55%) as particularly common and troublesome.¹⁶

Additional frequent problems include bone pain and difficulty thinking clearly, often called 'brain fog'.^{17,18} These cognitive difficulties, alongside emotional impacts such as worry, sadness and feeling demotivated, also represent a significant mental health burden that many patients experience daily.¹⁹ Further, the unpredictable release of chemicals can also cause potentially life-threatening severe allergic reactions known as anaphylaxis.¹³

This heavy burden of symptoms results in a significant reduction in health-related quality of life (HRQoL) in people with ISM and their caregivers.²⁰ The overall impact of the disease, measured using Disability-Adjusted Life Years (DALYs), is comparable to that of serious long-term conditions like lymphoma or psoriasis, with studies showing an average of 12.7 (± 5.9) symptoms per patient that markedly affect quality of life, emotional wellbeing and social functioning.²¹ Studies show that in people with ISM, physical and mental quality of life (QoL) scores are substantially impaired compared to healthy people.¹⁷ The European PRISM study found that systemic mastocytosis significantly damaged patients' mental health and functioning, with low average mental health scores of 42.2 for ISM, much lower than the typical healthy score of 50.1.¹⁷

People with ISM frequently report difficulty performing daily activities and interference with their social life.^{20,22} For people with ISM in the UK, 50% reported that ISM significantly affected their ability to work. This job impact resulted in 32% reducing their working hours, 16% voluntarily quitting their job and 18% going on medical disability.²³ This highlights the underlying burden requiring external support. The severe functional limitations, unpredictable symptoms and frequent need for multiple symptomatic therapies (called polypharmacy) mean there is also a considerable impact on the families and caregivers of patients with ISM.^{16,22,24}

ISM can also worsen over time progressing to more advanced forms, particularly in patients with increased serum tryptase levels and a high symptom burden. Notably a study showed that 15% of patients who initially had mild symptoms still experienced their disease worsening to a more severe symptom burden within two years.^{25,26}

The burden of symptoms and other health conditions (comorbidities) in people with ISM can increase the risk of death.²⁷ A Danish population-based study following 393 patients over 8 years found that people with ISM were about 1.5 times more likely to die during the study period compared to people without the condition.²⁷ This reduced life expectancy found in a Danish study is considered reflective of the patient population in the UK.¹¹ UK clinicians recognise that people with ISM have a higher risk of death compared to the general population. However, it is important to note that the severity of symptoms does not predict how long someone will live. Clinicians have found no significant difference in mortality between people with mild, moderate and severe ISM symptoms, showing that symptom severity does not correlate with life expectancy.¹¹

ISM does not have an effective standard of care treatment, as current therapies remain symptomatic. They only partly control the disease, do not fully manage symptoms and often cause side effects or complications.²³ There are no NHS-approved treatments for ISM that target the underlying *KIT D816V* mutation found in about 95% of ISM cases.¹⁰ Many people rely on potentially harmful off-label tyrosine kinase inhibitors (TKIs) or cytoreductive therapies and there is a clear unmet need for those with moderate-to-severe symptoms that are not adequately controlled.²⁸

Avapritinib, which NICE has already recommended for the treatment of patients with Advanced SM (AdvSM), targets the *KIT D816V* mutation and addresses the underlying disease process in ISM.^{5,29,30} Avapritinib (used alongside symptomatic management) is a potential treatment option for people with ISM who continue to have moderate-to-severe symptoms despite current treatment.

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?

Diagnosing ISM can be challenging and often takes several years, with many patients experiencing diagnostic delays of up to five years from when symptoms first appear. This delay occurs because the symptoms are often vague and can be mistaken for other more common conditions.²

The diagnosis is made using specific criteria established by the World Health Organisation and the International Consensus Classification. Doctors look for evidence of abnormal mast cells in various body tissues, particularly the bone marrow. The diagnostic process typically includes:^{10,31}

- Blood tests: Doctors measure the level of a protein called tryptase in the blood. People with ISM usually have elevated tryptase levels (above 20 ng/mL), which is one of the key diagnostic markers.
- Genetic testing: A blood test is performed to look for the *KIT D816V* mutation. Recent advances in testing methods have improved the ability to detect this mutation, even when it is present in very small amounts.
- Bone marrow biopsy: This procedure involves taking a small sample of bone marrow, usually from the hip bone, to examine under a microscope for abnormal mast cell collections.
- Additional tests: Doctors may also perform skin biopsies if there are visible skin lesions and various scans to check for organ involvement.

The diagnostic process can be physically and emotionally demanding for patients, requiring multiple hospital visits and invasive procedures.³² Many patients also struggle with having their symptoms taken seriously before receiving a proper diagnosis, which can add to their distress.² Before starting avapritinib, healthcare providers need to confirm that patients have moderate-to-severe symptoms that are not adequately controlled by other treatments. Importantly, avapritinib does not require any additional special diagnostic tests beyond those already used to diagnose ISM. However, doctors do need to consider the patient's heart function before starting treatment, as the medication can affect heart rhythm in some people.³³

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.

Currently, there are no approved therapies for the treatment of patients with ISM.¹⁰ There are no specific UK guidelines for managing ISM and NHS England provides general information about mastocytosis, but this covers all types of the condition rather than focusing specifically on the indolent form.³⁴ International guidelines from the European Competence Network on Mastocytosis (ECNM) recommend an individualised approach to treatment based on each patient's specific symptoms and needs due to the highly varied and unpredictable nature of ISM symptoms.³⁵ The current approach to treating ISM is based on managing each symptom individually rather than treating the underlying cause of the disease.³⁵

Typical medications used include:^{11,36,37}

For skin symptoms (itching, flushing, spots):

- H1 antihistamines (such as cetirizine) - used by nearly all patients (100%)
- Topical creams and ointments (47% of patients)
- Ultraviolet light therapy in some cases

For digestive symptoms (stomach pain, diarrhoea, nausea):

- H2 antihistamines like ranitidine (66% of patients)
- Proton pump inhibitors like omeprazole (28% of patients)
- Mast cell stabilisers such as sodium cromoglycate (35% of patients)
- Anti-diarrhoeal medications like loperamide (10-15% of patients)

For other symptoms:

- Leukotriene inhibitors like montelukast for breathing difficulties (35% of patients)
- Corticosteroids like prednisolone for severe symptoms (10% of patients)
- Bisphosphonates for bone problems
- Adrenaline auto-injectors for emergency allergic reactions (50% of patients)

When standard symptomatic treatments fail to provide adequate relief, doctors sometimes try off-label treatments (medicines used outside their official approval) such as interferon-alpha, omalizumab, cladribine or midostaurin. However, these are not routinely available and their effectiveness is limited.³⁵ Most patients require multiple medications simultaneously, with the average patient taking 4 different supportive care medications. This creates several problems including medication burden (polypharmacy) from managing multiple treatments, limited effectiveness as many patients continue to have troublesome symptoms despite multiple medications, increased side effects from taking several drugs, and potential drug interactions where medications can interfere with each other.^{2,20}

Avapritinib is intended for patients who have moderate-to-severe symptoms that remain inadequately controlled despite trying at least two different types of symptomatic treatments. Avapritinib would be used alongside continued standard of care, not instead of it.³³ However, clinical studies have shown that some patients were able to reduce or even stop some of their supportive care medications while taking avapritinib.³⁸ The US National Comprehensive Cancer Network (NCCN) guidelines now list avapritinib as a preferred treatment option for symptomatic ISM.³⁹

Avapritinib can interact with certain medications, particularly those that affect heart rhythm. Patients need careful monitoring if they are taking other medications that can affect the heart's electrical activity. The medication should be used with caution in patients with existing heart rhythm problems. Healthcare providers also need to consider the patient's kidney and liver function before prescribing avapritinib, as these organs help process the medication from the body.³³

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.

Several comprehensive studies have been conducted to understand the patient experience of living with ISM, providing valuable insights into the daily challenges, unmet needs, and QoL impacts faced by people with this condition.

PRISM Study^{2,17,40}

The largest patient-based evidence study was the PRISM survey, conducted across seven European countries including the UK. This cross-sectional survey used validated questionnaires including the SF-12, EQ-5D-5L and disease-specific assessment tools to collect data from 237 patients with ISM, including 50 patients from the UK. The study assessed symptom burden, QoL and the impact on daily activities through structured online surveys.

Key findings from the PRISM study showed that 67% of patients experienced moderate-to-severe symptoms, with 68% of UK patients falling into this category. The study revealed that patients rated the impact on their daily living as moderate, with many reporting they avoided leaving the house due to their symptoms (mean score 4.7 out of 7) and felt isolated (mean score 4.5 out of 7). A secondary analysis of the PRISM data further demonstrated profound socio-emotional impacts, with 48% of patients feeling that others did not understand their disease, 30% feeling anxious or worried about their condition and 27% feeling their disease was controlling their life. Significant disruptions to physical activity (44-65% of patients), work (37-61%) relationships (19-47%), and daily functioning were also reported, with patients experiencing moderate to severe symptoms reporting substantially greater impacts across all domains.

Mast Cell Connect Patient Registry¹⁶

The Mast Cell Connect Registry represents the first patient-reported registry specifically for Mastocytosis. This patient-reported registry used structured questionnaires to systematically collect data on symptom frequency, severity, and impact on daily functioning from 88 patients with moderate-to-severe ISM symptoms.

The registry findings, similar to the European PRISM study, showed that the most common symptoms were fatigue (experienced by 72% of patients) and abdominal pain (55% of patients). Over 80% of patients considered themselves limited in their ability to work or perform daily activities due to their symptom burden.

Qualitative study on patient experience⁴¹

A qualitative study conducted 90-minute virtual interviews with 18 adult patients in the United States who had a physician-confirmed diagnosis of non-advanced systemic mastocytosis, which includes ISM. Patients reported 32 different symptoms across multiple areas including skin, thinking and concentration (neurocognitive), gastrointestinal, fatigue and pain, aligning with the findings of the European PRISM study and the Mast Cell Patient Registry. More than half of patients (56%) had also experienced severe allergic reactions (anaphylaxis), and 27% reported reduced bone density.

One patient captured the daily reality of living with the condition:

"I'm constantly thinking about it, worried about it. I don't know every day what it's doing to my body...I see my list of foods shrinking and that scares me. I never know if I'm going to have a severe allergic reaction...I'm afraid to be anywhere too far from a toilet..."

Patient and healthcare provider perspectives¹⁹

A US study surveyed 53 ISM patients and 50 healthcare practitioners to compare perspectives on symptom burden and management. A notable gap emerged: only 24% of patients felt their

disease was well controlled, whilst 76% of healthcare providers believed most of their ISM patients had well-controlled disease.

Similar to other studies in Europe and the US, findings confirmed that symptoms like fatigue, brain fog and diarrhoea are the most common and challenging aspects of ISM, driving patients to seek medical care. The study further highlighted the diagnostic delay and treatment burden in ISM. Patients saw an average of 9 different healthcare providers before diagnosis, with an average 3-year delay from symptom onset to diagnosis. Most patients took multiple medications (41% took 1-5 medications, 40% took 6-10 medications and 19% took more than 15 medications), adding to daily burden of treatment.

TouchStone Survey²⁰

The TouchStone survey was a cross-sectional patient-reported outcomes study conducted in the US, which included 56 patients with systemic mastocytosis, of whom 66% had ISM. This study employed validated patient-reported outcome measures and structured interviews to assess the patient experience, treatment burden, and QoL impacts.

The study found that almost 64% of patients reported avoiding leaving the house due to their mastocytosis symptoms, highlighting the significant impact on social functioning and QoL.

UK-specific patient evidence⁴²

A symptom burden study was conducted at Guy's and St Thomas' NHS Foundation Trust, a UK centre of excellence for Mastocytosis. This single-centre observational study used the validated Indolent Systemic Mastocytosis-Symptom Assessment Form to systematically assess 76 patients with ISM over a 4-week period, collecting daily symptom severity scores.

The study found that 43% of patients had symptoms severe enough to meet the threshold for moderate-to-severe disease, with fatigue and skin spots being the highest-scoring symptoms.

Disease burden assessment⁴³

A comprehensive disease burden study was conducted at a French expert centre (CEREMAST) using DALYs to quantify the overall impact of ISM. This prospective and retrospective study used structured patient interviews, validated QoL questionnaires and disability assessment tools to systematically measure the cumulative years lost due to ill-health and disability.

The study found that patients reported an average of 12.7 symptoms, with disease burden comparable to serious conditions such as lymphoma, leukaemia, and psoriasis. The research highlighted marked effects on emotional and social wellbeing, emphasising the need for better disease management.

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.

Avapritinib represents a fundamentally different approach to treating ISM compared to current treatments. Instead of only managing symptoms, avapritinib targets the underlying genetic cause of the disease.⁴⁴

In about 95% of people with ISM, the condition is caused by a specific genetic change called the *KIT D816V* mutation. This mutation causes a protein called KIT to become constantly "switched on," leading to uncontrolled growth and activation of mast cells throughout the body.^{14,15,44,45}

Avapritinib works by specifically targeting and blocking this faulty KIT protein. Avapritinib is a type 1 tyrosine kinase inhibitor (a substance that blocks a function) that binds directly to the KIT protein and stops it from sending the signals that cause mast cells to multiply and become overactive.⁴⁴

Current standard treatments primarily treat the symptoms caused by the unchecked release of inflammatory chemicals (mediators). They might help with itching, stomach problems, or other specific issues, but they don't address why these symptoms are happening in the first place, the uncontrolled proliferation of mast cells driven by the *KIT D816V* mutation. Avapritinib directly targets this mutation.⁴⁴ Avapritinib is highly selective and potent against the specific *KIT D816V* mutation found in ISM. Laboratory studies show that avapritinib is very effective at blocking this particular mutation with an ability to inhibit the faulty protein at very low concentrations. This precision is important because it means the medication can effectively target the disease-causing mechanism while potentially having fewer effects on normal, healthy cells in the body.⁴⁴

Avapritinib received EU marketing authorisation in December 2023 as the first and only treatment for adult patients with ISM whose moderate-to-severe symptoms are inadequately controlled.³³

By targeting the root cause of the disease, avapritinib offers the potential for comprehensive disease control rather than just managing individual symptoms, allowing patients to experience improvements across multiple symptom areas simultaneously and potentially reduce their medication burden.³⁸

Regulatory Documents:

- European Medicines Agency (EMA) Summary of Product Characteristics (SmPC): Avapritinib Available from: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.
- In May 2023, avapritinib was approved by the FDA for the treatment of adult patients with ISM.⁷ US FDA Prescribing Information: AYVAKIT® (avapritinib) Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212608s013lbl.pdf (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212608s013lbl.pdf).

3b) Combinations with other medicines

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

- Yes

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.

Avapritinib is designed to be used in combination with existing symptomatic treatments, not to replace them entirely. This approach recognises that while avapritinib targets the underlying genetic cause of ISM (the *KIT D816V* mutation), patients may still benefit from continued symptomatic support, particularly during the initial treatment period as avapritinib begins to take effect.³³

All symptom-directed therapies (SDT) used alongside avapritinib are readily available through the NHS and include commonly prescribed treatments such as antihistamines (cetirizine), acid-reducing medications (omeprazole) and mast cell stabilisers (sodium cromoglycate)³⁴. These medications are available treatments with known safety profiles. The main side effects of continuing supportive care medications alongside avapritinib are those already associated with these individual treatments, such as drowsiness from antihistamines or stomach upset from some medications.^{11,33,35} Healthcare providers monitor patients carefully for any interactions between avapritinib and other medications, particularly those that might affect heart rhythm.³³

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 is taken as a simple oral tablet once daily at home, making it convenient for patients to manage their treatment independently. The tablet is taken preferably at the same time to maintain consistent levels of the medication in their body. The recommended dose is 25mg taken by mouth once daily, which should not be exceeded.^{1,33}

Avapritinib is intended as a long-term treatment, with clinical studies showing continued benefits over three years of treatment. The duration of treatment is determined by the patient's response and tolerability, with regular monitoring by their healthcare team.^{1,33}

Patients should be aware that avapritinib tablets should be swallowed whole and can be taken with or without food. If a dose is missed, patients should take it as soon as they remember on the same day, but should not take two doses on the same day to make up for a missed dose.

Healthcare providers will monitor patients regularly, particularly during the initial months of treatment, to assess response and manage any side effects. This monitoring can typically be done during routine clinic visits without requiring additional hospital admissions.^{1,33}

The once-daily, oral administration method of avapritinib offers a potentially significant advantage regarding patient and caregiver burden compared to existing management strategies.^{2,46} Standard care for ISM often involves concurrent symptom-directed therapies, leading to a burden of polypharmacy where patients commonly take multiple medications daily.^{2,38} In contrast, avapritinib is a single, targeted therapy designed to treat the underlying cause of the disease.³⁸

Evidence from the PIONEER clinical trial demonstrated that this approach successfully reduced the need for other medications; 21% of patients treated with avapritinib were able to decrease their usage of supportive medications and 3% achieved complete discontinuation of supportive treatment, results that were higher than in the placebo group.^{2,38,46}

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 PIONEER trial ([NCT03731260](#)) is the pivotal clinical study supporting avapritinib for ISM. This is a comprehensive three-part, randomised, double-blind, placebo-controlled study conducted at 42 sites, primarily in Europe (23 sites) and North America (19 sites).^{18,46}

Study population:

Adults aged 18 years and older with centrally confirmed World Health Organisation diagnosis of ISM who had moderate-to-severe symptoms (symptom score of 28 or higher on the ISM-SAF) despite optimised treatment with at least two symptom-directed therapies.

Study design and size:

Part 1 (dose selection): 39 participants tested three different doses of avapritinib (25mg, 50mg, 100mg) versus placebo to determine the best dose

Part 2 (main study): 212 participants (141 receiving avapritinib 25mg, 71 receiving placebo) in a randomised comparison over 24 weeks

Part 3 (long-term extension): Ongoing open-label study following participants for up to 5 years to assess long-term safety and effectiveness with an estimated completion date of January 31, 2028.

Key inclusion criteria:

Patients must have had inadequate symptom control despite optimised therapy with at least two symptomatic therapies, stable corticosteroid dose if applicable and good performance status.

Key Exclusion Criteria:

Patients with other forms of mastocytosis, prior avapritinib treatment, recent cancer treatments, or significant heart rhythm abnormalities were excluded.

Key publications:

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. NEJM Evidence. 2023;2(6):EVIDoA2200339.⁴⁶

Trial Registry Information:

Full details are available at ClinicalTrials.gov using identifier [NCT03731260](#).

Other Relevant Research:

While PIONEER is the main clinical trial for avapritinib in ISM, several important supporting studies have been conducted. These studies provide additional insights into specific aspects of avapritinib treatment that are particularly relevant to patients with ISM, such as bone health and allergy management, which are common concerns in this patient population.

- Bone Health sub-study: A specialised analysis within PIONEER examining the effects of avapritinib on bone mineral density in patients with ISM, with preliminary results presented at medical conferences.⁴⁷
- Anaphylaxis analysis: An exploratory study examining the impact of avapritinib on severe allergic reactions in a subset of PIONEER participants who experienced anaphylaxis.⁴⁸

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.

The effectiveness of avapritinib was mainly studied in a key clinical trial called PIONEER, which compared 25 mg avapritinib to placebo (a dummy pill). Both groups also received standard of care treatment for managing symptoms, such as antihistamines.

The main measure of how well avapritinib worked was the change in the Total Symptom Score (TSS) from the ISM-SAF, which is a specific questionnaire designed to measure symptom severity in this condition.^{18,46}

For patients living with ISM, symptom reduction is typically the most immediately important outcome, as symptoms significantly impact daily life and overall wellbeing. The improvements in skin symptoms (spots, itching, and flushing) may be particularly meaningful as these are visible symptoms that can affect social interactions and self-confidence. The reductions in disease markers (tryptase, KIT mutation levels, bone marrow mast cells) may be important to patients concerned about disease progression, as these objective measures suggest the treatment addresses the underlying disease process.^{18,46} The ability to reduce other medications is also meaningful for patients managing complex medication regimens and experiencing side effects from multiple treatments.^{18,38}

Effectiveness compared to current treatments at 24 weeks

Avapritinib significantly reduced overall symptom severity over 24 weeks compared to placebo.^{18,46} At 24 weeks, participants taking avapritinib reported a mean reduction of 15.6 points in their TSS, compared to a reduction of 9.0 points for those taking placebo.^{18,46}

A clinically important response was defined as at least a 30% reduction in the TSS. A greater proportion of participants treated with avapritinib achieved these meaningful improvements compared to those on placebo. Specifically, 45.4% of avapritinib-treated participants achieved at least a 30% reduction in symptoms, compared with 29.6% of placebo participants.^{18,46}

Furthermore, 24.8% of participants on avapritinib achieved a substantial improvement (at least a 50% reduction in symptoms), compared to 9.9% on placebo. The domain concerning skin symptoms showed the most pronounced improvement when comparing avapritinib to placebo.¹⁸

Avapritinib also showed effectiveness in controlling the underlying disease.^{18,46} Objective measures that track the physical signs of the disease were significantly reduced in the avapritinib group. For instance, 53.9% of participants on avapritinib achieved a 50% or greater reduction in serum tryptase levels (a common disease marker), compared to 0% of participants on placebo. Avapritinib also significantly reduced the level of the *KIT* D816V mutation (the genetic defect causing the disease) and the percentage of mast cells in the bone marrow.^{18,46}

Anaphylaxis and reduction in other medications

Additional exploratory analyses suggested that avapritinib may reduce the frequency of severe allergic reactions (anaphylaxis). Specifically, 75% of patients who had experienced anaphylaxis before treatment had no events during the 24-week treatment period. These findings were based on a small sample size (13 participants), so larger studies would be needed to confirm this benefit.⁴⁸

Furthermore, avapritinib allowed patients to reduce their use of other symptom-directed medications (standard of care polypharmacy). At 24 weeks, 21% of avapritinib-treated patients decreased their standard of care usage, and 3% were able to stop these medications entirely, compared to 13% and 0%, respectively, in the placebo group.^{18,38}

Long-term efficacy

Long-term data from the ongoing open-label extension part of the PIONEER trial (Part 3) confirmed that the benefits observed in symptom reduction, disease control and QoL were sustained through up to 3 years of treatment.^{49,50} During this long-term follow-up, sustained reductions were maintained in the TSS and objective markers like serum tryptase levels and the *KIT D816V* mutation level.^{49,50}

Exploratory bone health tests were also conducted. Many patients with ISM also experience bone-related problems, including osteopenia (lower than normal bone density) and osteoporosis (significantly weakened bones that are at higher risk of fracture). In the PIONEER trial, nearly half of the enrolled patients had bone-related conditions at the start of the study.⁵¹

In a small exploratory study of 13 patients who had bone density scans before and after two years of avapritinib treatment, improvements in bone mineral density were observed. On average, patients showed increases of 4.8% in the lower spine and 3.6% in the hip bone (femoral neck). Improvements of this magnitude are associated with reduced risk of bone fractures in patients with osteoporosis. However, because this finding comes from a small number of patients at a single study site, larger studies are needed to confirm whether avapritinib consistently improves bone health in patients with ISM.⁵¹

Limitations to the data

The study population in PIONEER was mainly female (70.9% to 76.1%), under 65 years of age (84.5% to 93.6%) and White (77.3% to 85.9%). This may limit how fully the results apply to patients from more diverse backgrounds.^{18,49} However, clinical experts did state that the PIONEER trial population is comparable the UK general population.¹¹

The core comparison against placebo lasted 24 weeks. The long-term data (Part 3) came from an open-label extension, meaning participants and researchers knew who was receiving avapritinib, which can make the interpretation of patient-reported symptom improvements potentially complicated due to the removal of the placebo control.^{18,49} However, the durability of objective markers (tryptase and *KIT D816V* VAF) provided reassurance that the underlying disease control was maintained.^{49,50} A proportion of patients did not achieve adequate symptom control on the starting dose of 25 mg and required a dose increase to 50 mg due to higher symptom burden. This suggests that some people with ISM may benefit from dose escalation to manage their symptoms more effectively.^{49,50}

Minor protocol deviations occurred in the study, with a higher rate in the avapritinib group in Part 2, but none were judged to have affected the integrity of the data.¹⁸ Subgroup analyses also indicated minor numerical differences in symptom reduction based on gender or baseline serum tryptase levels, but the small number of participants in these subgroups means no firm conclusions can be drawn.¹⁸ The study focused on patients with moderate to severe symptoms (ISM-SAF TSS $\geq$ 28), so the results may not apply to those with milder symptom presentations.^{18,49}

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.

HRQoL measures how a disease and its treatment affect a patient's well-being, including their physical health, emotional state and ability to participate in social life and daily activities. For

people living with ISM, symptoms are broad and unpredictable, leading to a considerable burden on HRQoL and difficulties in everyday life.^{17,19,23,42}

Due to the unique and varied nature of ISM symptoms, which generic health questionnaires often fail to capture, a specific tool called the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) was developed with input from patients and disease experts to measure symptom severity. The ISM-SAF is considered a validated tool completed by patients in clinic.^{52,53}

In addition to the ISM-SAF (which measures symptom severity), avapritinib effectiveness was evaluated using several established QoL questionnaires in the PIONEER trial.^{18,46}

- Mastocytosis Quality of Life questionnaire (MC-QoL): A disease-specific tool with 27 items, where lower scores indicate better quality of life.
- Patient Global Impression of Change (PGIC) and Severity (PGIS): Measures a patient's impression of how severe their condition is and how much it has changed.
- 12-Item Short Form Health Survey (SF-12): A general health questionnaire measuring physical and mental health components.
- EuroQoL 5-Dimension 5-Level questionnaire (EQ-5D-5L) and Visual Analogue Scale (EQ-VAS): General tools used to assess health status and QoL, where higher scores indicate better health.⁵⁴

The creation and validation of the ISM-SAF specifically demonstrates that the unique and heterogeneous symptoms of ISM cannot be fully captured through generic questionnaires alone. Therefore, the specialised measures like the MC-QoL and ISM-SAF provide supplementary and necessary information.^{18,46} Avapritinib demonstrated improvements across multiple measures of HRQoL, measured using several validated questionnaires:

- Disease-specific quality of life (MC-QoL): Participants taking avapritinib reported greater improvement across all domains of the MC-QoL compared with placebo at Week 24. The most significant mean percentage reductions (improvements) were seen in the emotions score (-41.47%) and the social life/functioning score (-38.52%). Long-term data confirmed these improvements were maintained over 3 years of treatment, with mean reductions of approximately 18 to 20 points in the MC-QoL total score.^{18,46,49}
- Patient impression of change (PGIC): At 24 weeks, patients on avapritinib reported "moderate improvement" on average (score 4.3), whilst those on placebo reported only "minimal improvement" (score 2.8).^{18,46}
- SF-12 health survey: Patients on avapritinib showed a 20.0% improvement in physical health scores and 12.3% improvement in mental health scores, compared to 12.1% and 6.3% respectively for placebo.^{18,46}
- EQ-5D-5L: Patients on avapritinib improved by an average of 6.6 points (18.5% improvement), whilst those on placebo improved by only 0.1 points (4.5% improvement).¹⁸ These improvements in EQ-5D-5L scores were sustained through 3 years of follow-up.⁴⁹

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 dose of avapritinib used (25 mg once daily) was specifically chosen because it showed effectiveness similar to higher doses but was better tolerated, suggesting a favourable benefit-risk

profile for long-term treatment. The overall safety profile of avapritinib 25 mg taken once daily was similar to that of the placebo during the 24-week blinded portion of the trial (PIONEER Part 2).^{18,46,55}

- A high percentage of participants experienced at least one side effect in both groups: 90.8% of those taking avapritinib compared to 93.0% of those taking placebo.
- Side effects considered related to the study drug occurred in 54.6% of participants taking avapritinib versus 45.1% of participants taking placebo.
- Serious side effects were reported less frequently in the avapritinib group (5.0%) than in the placebo group (11.3%). Importantly, no serious side effects were considered related to the study drug in either group during this period.

Most common side effects (occurring in 10% or more of treated patients):^{18,46}

Side effect	Avapritinib (N=141)	Placebo (N=71)
Headache	19.1%	19.7%
Nausea	12.8%	16.9%
COVID-19	12.1%	11.3%
Dizziness	11.3%	8.5%
Diarrhoea	10.6%	11.3%

Specific side effects requiring consideration:

Oedema (Swelling): Swelling, particularly face oedema (swelling of the face), was reported more frequently in the avapritinib group than in the placebo group.^{18,46}

- Overall swelling events (oedema) affected 25.5% of avapritinib participants compared to 11.3% of placebo participants.
- Face oedema was the only side effect that occurred with more than a 5% difference between avapritinib (7.1%) and placebo (1.4%).
- Most of these swelling events were mild or moderate in severity (Grade 1 or 2).
- Healthcare providers should consider the risk for localised oedemas before treating with avapritinib.

Cognitive Effects: Events affecting memory or concentration were infrequent.^{18,46}

- Side effects related to cognitive function occurred in 2.8% of avapritinib participants compared to 4.2% of placebo participants.
- Memory impairment was reported in 1.4% of participants in both the avapritinib and placebo groups.
- Healthcare providers should consider the risk for worsening cognitive effects in patients with ISM before administering avapritinib.

Management of side effects and treatment adjustments

When a side effect occurs, doctors may manage it by temporarily stopping the medication (interruption), reducing the dose or permanently stopping the treatment (discontinuation).^{18,46}

Treatment adjustments (PIONEER Part 2, 24 Weeks):^{18,46}

- Interruption: Side effects led to the interruption of the study drug in 8.5% of avapritinib participants versus 12.7% of placebo participants.
- Dose Reduction: Side effects led to dose reduction in a very small percentage of participants: 1.4% in the avapritinib group and 1.4% in the placebo group.
- Discontinuation: Side effects led to the permanent discontinuation of the study drug in 2.1% of avapritinib participants versus 1.4% of placebo participants.

Long-term safety

During the open-label extension (Part 3) of the PIONEER trial, with a mean treatment duration of over three years (37.1 months) for participants who started on the 25 mg dose, no new safety signals were observed. Across the entire study period (including Parts 1, 2, and 3), the rate of people stopping avapritinib due to a side effect remained low, at 6.2% for the 25 mg starting dose population.⁴⁹

The full product information, including a complete list of known side effects, is detailed in the SmPC for avapritinib, available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.⁵⁵

The MHRA marketing authorisation details are included in Appendix A of the submission.¹ Avapritinib received EU marketing authorisation in December 2023.⁶

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

The key benefit of avapritinib is that it is a disease-modifying treatment that targets the underlying cause of the condition, rather than just managing the unpredictable and severe symptoms. Current treatments, only aim to control symptoms, but often fail to provide adequate relief.^{10,38}

Avapritinib directly targets the *KIT D816V* mutation present in approximately 95% of people with ISM, addressing the root cause rather than just treating symptoms. It is more potent and selective against the *KIT D816V* mutation compared to other TKIs which are sometimes used off-label.^{11,46,56}

In clinical studies, avapritinib significantly reduced ISM symptoms and improved QoL (living day-to-day) in people with ISM, with benefits maintained and treatment well tolerated over three years of treatment.^{18,46,49}

In addition, avapritinib is taken as a single 25 mg tablet once daily by mouth, more convenient than multiple medications at different times without needing injections or hospital visits, reducing the burden of treatment for people with ISM and their caregivers.⁵⁵

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

- Ongoing daily treatment is required to maintain benefits, as stopping would likely result in symptom return, representing a long-term commitment to administration alongside symptomatic therapies.^{18,49}

- There is limited evidence on avapritinib in diverse populations as the trial included predominantly female (70.9-76.1%), white (77.3-85.9%) and under-65 patients (84.5-93.6%), with only 24 weeks of placebo-controlled comparison, though the overall safety profile remains better than many drug alternatives not made specifically for ISM.^{18,49}

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 an important part of the NICE appraisal process. The PIONEER trial ([NCT03731260](#))⁵⁷ for ISM only follows patients for a limited period, therefore the model helps to predict what might happen over a long time. It looks at the overall health benefits and the NHS costs of each treatment over a patient's lifetime.⁵⁸

For this appraisal, a cost-effectiveness model (CEM) was developed to compare the costs and health benefits of avapritinib compared to the current SDT, where symptomatic therapies are the available clinical practice.^{34,58} While there is no specific UK or NHS clinical guidance for the management of patients with ISM, clinical experts confirmed, in their experience, the use of SDT including antihistamines (H1-/H2-blockers), proton-pump inhibitor (omeprazole), and leukotriene inhibitor (montelukast), corticosteroid (prednisolone), mast cell stabilisers (cromolyn sodium), and monoclonal antibody (omalizumab). In some cases, patients with more severe or advanced disease may require using off-label TKI treatment, such as midostaurin, imatinib and dasatinib.^{10,11,39}

The CEM follows a group of patients aged 40 and over with ISM as they move through three ISM health states (mild, moderate and severe).^{11,58} These health states are based on symptom severity and reflect how the condition can impact patients, with each health state represented by a utility score for the patient and cost to the NHS.⁵⁸ Additionally, the model also includes two progression states of smouldering systemic mastocytosis (SSM) and AdvSM, reflecting the clinical possibility (albeit very low)^{4,59} for ISM patients to progress to a more advanced disease, and an absorbing state of death.⁵⁸

At regular monthly intervals, the model estimates whether patients stay in the same health state or move to another. This structure reflects the chronic and progressive nature of ISM and helps to assess the long-term impact of avapritinib on symptoms, disease progression, QoL, and NHS costs.⁵⁸

Modelling how much a treatment extends life

- ISM is a chronic condition with uncertainty as to the drivers of mortality and progression to more advanced disease states (SSM and AdvSM). Therefore, it is difficult to assess the long-term impact of avapritinib on progression to SSM and/or AdvSM, and mortality.⁵⁸

- No direct mortality benefit has been applied for avapritinib versus SDT within the ISM health states. Mortality differences may be expected based on the rate of transition to SSM and AdvSM.⁵⁸
- The proportion of patients expected to transition to SSM and AdvSM is expected to be small and therefore would not be a driver of results in the model.^{4,59} Scenarios are used to test assumptions regarding the impact of avapritinib on the rate of progression to these more advanced disease states.⁵⁸

Modelling how much a treatment improves quality of life

- The PIONEER trial showed that treatment with avapritinib reduced symptom severity and achieved a quicker and longer response for patients with ISM.^{18,49} In the model, this improvement was reflected as a higher QoL compared with patients receiving the SDT. Adverse events were also included in the model to ensure a balanced estimate of its overall impact.⁵⁸
- QoL data for ISM were derived from the EQ-5D-5L questionnaire in the PIONEER trial were applied to the model to estimate changes in HRQoL over time.^{18,46} These data were used to calculate the overall health benefit, expressed as quality-adjusted life years (QALYs).⁵⁸
- As utility data for SSM and AdvSM health states were not included in the PIONEER trial. Therefore, alternative QoL data sources for SSM and AdvSM were identified.^{2,60}
- Avapritinib is expected to improve QoL by reducing symptom and mast-cell burden, helping patients move to and remain in stable disease states.³¹

Modelling how the costs of treatment differ with the new treatment

- The drug cost of avapritinib plus SDT is expected to be higher than the current cost of SDT used in the NHS. Avapritinib is expected to reduce the requirement for SDT treatments but not entirely replace these treatments.⁵⁸
- Avapritinib is expected to reduce other healthcare costs by reducing symptom burden and lowering the requirement for excess health care resource use.⁵⁸

Uncertainty

- As per UK experts' experience, different healthcare resource use between treatment responders and non-responders is assumed. The model assumed that healthcare resource use is reduced by 25% for patients who respond to treatment with avapritinib ($\geq 30\%$ reduction in TSS).^{11,58}
- The duration of treatment for avapritinib is based on real-world evidence (RWE) due to the limited PIONEER trial period. A US cohort extended study was incorporated into the model to extrapolate long-term effectiveness in the absence of UK RWE data.^{18,49,58,61}
- No mortality data was observed for ISM from the PIONEER trial, thereby mortality hazard ratios versus general population from literature sources were validated by UK clinical experts.^{27,62}

Results

The results of the model suggest that treatment with avapritinib provides greater clinical benefits for an increased cost the NHS. Avapritinib is expected to be a cost-effective alternative to the current SDT regimen used in the NHS.⁵⁸

Additional factors

- A severity modifier is applied because moderate-to-severe ISM causes long-term and unpredictable symptoms such as fatigue, pain, and gastrointestinal problems, which can

seriously affect QoL. Severity modifiers help NICE categorise how serious a health issue is and how it influences the value of different healthcare interventions or treatments.⁶³

- End-of-life cost was not considered in the model, as per UK experts' experience, there is no significant mortality difference between ISM patients and the general population.¹¹
- Avapritinib has a simpler administration route compared with the current SDT, which may demonstrate better patient adherence. However, in the absence of real-world data and UK experts' experience, this potential benefit was not considered within this submission.¹
- One limitation of this submission lies in the limited data availability. In the absence of long-term trial data and UK RWE data, the model incorporated the US Speciality Pharmacy and PAP ISM patient RWE dataset for estimating long-term efficacy. This may not fully represent the UK population. However, the extrapolation to the real world was validated by the UK experts' experience.⁶¹
- Avapritinib is taken orally once a day, whereas the current SDT may require multiple different medicines to control symptoms. Because avapritinib is a single treatment, patients may find it easier to follow the administration routes, and it also may simplify clinical management for patients and reduce the overall treatment burden.¹ Given the difficulty in assessing the impact of this, this remains an uncaptured burden in the model.

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)

Innovation:

Compared to available management of ISM employed by the NHS, avapritinib represents a significant shift in this burdensome disease's treatment paradigm.¹¹ Avapritinib's disease-modifying effects stem from its high affinity for the *KIT D816V* mutation (compared to other TKIs) and the tackling of ISM's underlying pathophysiology.^{1,31} As shown by the PIONEER trial, avapritinib's sustained ability to reduce mast cell burden, improve symptoms and patient HRQoL is strongly indicative of a disease-modifying effect, especially with long-term clinical efficacy reported up to 3 years.^{1,46,50,64,65}

QALY benefits not captured in the economic model:

Unlike the key outcomes (symptom severity, mast cell burden and HRQoL), exploratory outcomes from the PIONEER clinical trial were not included in the model.¹¹ These uncaptured benefits include reductions in anaphylactic episodes (severe allergic reactions), usage of SDT and bone-related issues with the drug compared to control-treated patients (placebo group).^{38,48,51} These improvements were seen in a small number of patients compared to the key outcomes, hence their use as supporting evidence only.¹⁸

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 (another TKI which is off-label for ISM), 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.⁶⁶

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 ISM 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 of avapritinib in patients with ISM:

PIONEER clinical trial references:

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. NEJM Evid. 2023;2(6):EVIDoa2200339.

PRISM study references:

Triggiani M, Hobart J, Alvarez-Twose I, et al. Patient-Reported Outcomes and Provider Perceptions of Systemic Mastocytosis: Results From the PRISM Study. Clin Exp Allergy. 2025;55(9):784–794.

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

AdvSM	Advanced systemic mastocytosis
CEM	Cost-effectiveness model
DALY	Disability-Adjusted Life Years
ECNM	European Competence Network on Mastocytosis
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-Dimension 5-level questionnaire
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IRP	International recognition procedure
ISM	Indolent systemic mastocytosis
ISM-SAF TSS	ISM Symptom Assessment Form Total Symptom Score
MC	Mast cell
MC-QoL	Mast cell quality of life
MHRA	Medicines and Healthcare products Regulatory Agency
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health Care and Excellence
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRISM	Perceptions Realities and Insights on Systemic Mastocytosis
PRO	Patient reported outcomes
QALY	Quality-adjusted life years
QoL	Quality of life
RWE	Real-world evidence
SDT	Symptom-directed therapy
SM	Systemic mastocytosis
SSM	Smouldering systemic mastocytosis
TKI	Tyrosine kinase inhibitors
TSS	Total Symptom Score

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avapritinib for treating uncontrolled moderate to severe indolent systemic mastocytosis [ID6578]

Clarification questions

December 2025

File name	Version	Contains confidential information	Date
ID6578_Avapritinib_EAG_CQs_[CON]_21Jan2026	FINAL	Yes	21.01.26

Section A: Clarification on effectiveness data

Decision problem

A 1. Priority. The population is described in Table 1 as: “Adults with inadequately controlled moderate to severe indolent systemic mastocytosis as per marketing authorisation and PIONEER trial population.”

- a) Please describe precisely how the marketing authorisation and the PIONEER trial define the population, noting any differences between the marketing authorisation and the trial.**

The marketing authorisation (expected in Q1 2026) indicates avapritinib (Ayvakyt®) for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.¹

For the PIONEER trial, patients were enrolled provided eligibility were fulfilled including criteria not specified in the marketing authorisation as per clinical trial conditions.^{2,3} These included an ISM-Symptom Assessment Form (SAF) Total Symptom Score (TSS) score of 28 or greater at screening (moderate to severe) and a failure to achieve symptom control for 1 or more baseline symptoms with at least 2 optimised symptomatic therapies (including H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab) with a stable dose for ≥ 14 days before the ISM-SAF eligibility criteria.^{2,3} Patients had a confirmed ISM diagnosis (via World Health Organisation [WHO] diagnostic criteria) with no organ damage C-findings and < 2 B-findings. Additionally, for those patients receiving corticosteroids, the dose must have been ≤ 20 mg/d prednisone and stable for ≥ 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. All patients were also required to have an Eastern Cooperative Group (ECOG) PS of 0 to 2.^{3,4}

In terms of exclusionary criteria in the PIONEER trial, these included the following conditions < 14 days preceding the ISM-SAF eligibility TSS assessment: any diagnosis of other WHO SM subclassifications (cutaneous mastocytosis only,

smouldering SM, SM with associated haematologic neoplasm, aggressive SM, mast cell leukaemia, or mast cell sarcoma), prior treatment with avapritinib, and no prior cytoreductive therapy including but not limited to masitinib and midostaurin, or investigational agent for <14 days or 5 half-lives of the drug (whichever is longer), and for cladribine, interferon-alpha, pegylated interferon, or antibody therapy <28 days or 5 half-lives of the drug (whichever is longer).²⁻⁴ Additionally, patients were not to have received radiotherapy or psoralen and ultraviolet A (PUVA) therapy or haematopoietic growth factor. Also, patients were not to have a QT interval corrected using Fridericia's formula (QTcF) of >480 msec.²⁻⁴

- b) If there are differences between the marketing authorisation and the trial, then please clarify that the former will determine the eligible population in English clinical practice.**

All information regarding PIONEER eligibility criteria was included in marketing authorisation documentation (Summary of Product Characteristics) and there is alignment in the indicated patient population.¹ NHS clinical practice is expected to follow the marketing authorisation for avapritinib in patients, as confirmed by clinical experts, which is based on the PIONEER pivotal trial.⁵

- c) As per the established World Health Organisation (WHO) criteria, patients exhibiting <2 B-findings and no C-findings are diagnosed with indolent systemic mastocytosis (ISM), which are also criteria for inclusion in the PIONEER trial. Please clarify if only patients who fulfil these criteria or whether patients diagnosed with ISM according to other criteria would be eligible for avapritinib in UK clinical practice.**

Only patients with a confirmed ISM diagnosis (according to WHO 2022 systemic mastocytosis criteria; see CS Section 1.3.3) will be eligible for avapritinib in UK clinical practice in England.^{6,7}

- d) Moderate to severe symptoms is defined in PIONEER based on a minimum mean TSS of ≥ 28 on the ISM-Symptom Assessment Form (ISM-SAF) over a 14-day eligibility screening period. Please clarify if only patients who fulfil this criterion or whether patients categorised as having**

moderate to severe symptoms according to other criteria would be eligible for avapritinib in UK clinical practice.

ISM-SAF will be available for NHS clinical practice for gauging the severity of patients with ISM and their response to treatment. Clinical experts have highlighted that ISM-SAF is a validated measure of symptom burden which informs expert judgement alongside measures of serum tryptase and KIT mutation (quantitative objective measures).⁵

The ISM-SAF was developed specifically to assess a key endpoint in clinical studies, addressing the lack of standardised symptom measurement tools for ISM.⁸⁻¹¹ It reflects the core symptoms identified in collaboration with leading clinical experts as most clinically meaningful to patients. Across multiple evidence sources including observational research, clinical trials, patient surveys, and real-world practice findings consistently support ISM-SAF TSS ≥ 28 as an appropriate threshold for moderate to severe ISM-related symptoms.^{2,12-14} Through real-world validation exercises in patient cohorts and clinical expert engagement, judgement in specialist clinics is informed by objective measures of mast cell burden and bespoke measures of symptom burden (ISM-SAF).⁵

As the marketing authorisation does not specify ISM-SAF (or the threshold score of ≥ 28 TSS), this is not required implicitly as criteria for moderate to severe patients with ISM. This tool does and will not dictate clinical practice but qualitatively informs management of patients alongside expert judgement and more quantitative measures.

e) Please describe the implications for clinical effectiveness and cost-effectiveness of any differences between the diagnosis of ISM and as having moderate to severe symptoms according to the criteria used in PIONEER, and any other criteria used in UK clinical practice.

Clinical and cost-effectiveness are based on PIONEER clinical trial data and ISM-SAF derived health states (mild, moderate, and severe). NHS clinical practice in England and Europe is aligned with the eligibility criteria of the PIONEER pivotal trial which is currently conducted in 3 sites in the UK (as part of the OLE phase).^{5,13} Clinical practice in the UK is informed by clinician judgement and expertise informed

by objective measures of mast cell burden as well as patient-reported outcome measures (including ISM-SAF, the specifically designed tool for patients with ISM).⁵ As such there is alignment between diagnostic criteria used in the PIONEER trial and NHS clinical practice, hence no discernible implication on clinical or cost-effectiveness.

A 2. Priority. Table 1 shows that avapritinib is as an add-on to standard care, and that the comparator is established clinical management without avapritinib. However, Figure 1 shows that avapritinib is accompanied by best supportive care, and lists the following treatments in the final branch of the therapeutic pathway: interferon-alpha, omalizumab, cladribine, TKIs and best supportive care. Also, the term “symptom-directed therapy (SDT)” is also used, in the company submission, including in the PIONEER trial.

- a) Please clarify whether established clinical management is intended to be synonymous with standard care, and SDT. If not then please describe precisely how these terms differ, and which one describes precisely the comparators to avapritinib.**

Established clinical management is equivalent to symptomatic-directed therapy (SDT) as noted throughout the submission. In published studies of patients with ISM (Gotlib et al. [2023]), best supportive care (BSC) is the terminology used to describe this ‘standard care’ basket. This submission has aligned BSC to SDT to better reflect the nature of these symptomatic therapies and individual patient needs according to heterogeneous and evolving symptomatology. SDT, unlike avapritinib, does not tackle the underlying pathophysiology of ISM.

- b) Please list all treatments in UK clinical practice that patients eligible for avapritinib currently receive, noting whether avapritinib would be added to them or would replace them.**

Patients with moderate to severe ISM are currently managed in UK clinical practice with symptomatic treatments including H1-/H2-blockers (antihistamines), proton-pump inhibitors (PPI), leukotriene inhibitors, corticosteroids, mast cell stabilisers, anti-diarrhoea medication, and off-label omalizumab (monoclonal antibody).^{5,15}

Avapritinib would be administered alongside these SDT options, it is not intended to replace symptomatic treatments.

- c) Please clarify whether each of these treatments are mutually exclusive i.e. could be given to the same patients, or whether at least some would be given to distinctly different patient subgroups of the population of those eligible for avapritinib.**

Due to heterogeneous symptom burden of ISM (particularly moderate to severe), patients are typically managed long-term with multiple concurrent SDT directed by clinician judgement.¹⁶⁻¹⁹ Symptoms may be spread across several organ systems, necessitating multiple relief measures including systemic medications, consequently associated with drug interactions, adverse events, and polypharmacy burden.^{12,20,21} There is no evidence to suggest that particular subgroups of patients receive particular therapies, symptom relief is dependent on the heterogeneous clinical symptomatology and patient's clinical condition.¹⁹

- d) Please provide justification as to why cladribine and interferon were not included as a relevant comparators, specifically in basket of SDT in the economic evaluation, given that they are listed as being used in UK clinical practice.**

While cladribine and interferon may be used as off-label therapies in select patients with ISM (as per clinical guidance)^{18,22}, clinical experts did not identify these therapies as part of the SDT in UK clinical practice.⁵ During the PIONEER trial, the use of antineoplastic or cytoreductive agents, such as interferon, cladribine, or off-label TKIs were part of exclusion criteria before trial baseline.² Therapy usage was prohibited less than 28 days before ISM-SAF eligibility assessment period, therefore, these are not considered SDT in the context of the clinical trial.²³ Clinical experts confirmed that cladribine and interferon were not considered part of the SDT management in clinical practice, hence their exclusion from the economic model.^{5,24}

- e) Please include comparative clinical effectiveness evidence (efficacy and safety data) and a cost-effectiveness analysis of avapritinib as it would be administered in clinical practice versus all treatments currently received by patients in UK clinical practice who are eligible for avapritinib.**

Avapritinib is administered as an add-on to SDT, and not by itself, to target the underlying *KIT D816V* pathophysiology of ISM rather than just alleviating symptoms.²⁵⁻²⁷ Comparative clinical effectiveness (efficacy and safety data) is derived from the pivotal Phase 2 PIONEER trial, which compared avapritinib 25 mg once daily plus SDT versus placebo plus SDT [See Section B2.1; Section B2.4.1]. In PIONEER Part 2, avapritinib plus SDT demonstrated a statistically significant mean reduction from baseline in the ISM-SAF TSS of -15.58 compared to -9.15 for SDT alone (difference: -6.43; 95% CI: -10.90, -1.96; p=0.003) at Week 24 [See Section B2.7.2.1]. Furthermore, 24.8% of patients receiving avapritinib plus SDT achieved a $\geq 50\%$ TSS reduction compared to 9.9% of those on SDT alone (p=0.005) [See Section B2.7.2.2].⁴ The safety profile was comparable between groups, with 90.8% and 93.0% of patients experiencing at least one adverse event (AE), respectively; the most common AEs ($\geq 10\%$) were headache, nausea and dizziness [See Section B2.11.2].^{2,4}

The cost-effectiveness analysis, based on a lifetime horizon and 3.5% discount rate, indicates that avapritinib plus SDT provides an incremental gain of 0.62 quality-adjusted life years (QALYs) [See Section B3.3.4; Section B3.10.1]. At the Patient Access Scheme (PAS) price, avapritinib is dominant versus SDT, providing greater health benefits at a lower total cost (incremental cost: [REDACTED]) [See Section B3.10.1.2]. Key model drivers include an average time on treatment (ToT) of [REDACTED] years and health state occupancy informed directly by observed PIONEER trial data [See Section B3.4.3.1; Section B3.3.3].^{28,29}

Systematic review

A 3. Priority. Table 7 of Appendix B includes studies of some treatments that are listed as potential comparators according to Figure 11 of the CS and/or SDT. Please present a comparison between the efficacy (in terms of ISM symptoms and mast cell burden) and safety of SDT in PIONEER and that observed in these clinical trials, noting whether each treatment was included in PIONEER or not.

Within the PIONEER trial, SDT, also referred to as BSC, represents the established clinical management and was utilised as the control arm for comparison with

avapritinib.² Currently, no single therapeutic agent is approved or reimbursed specifically ISM in England; therefore, the SDT basket reflects the standard clinical management directed solely at alleviating symptom burden.¹⁵

Regarding the efficacy in terms of ISM symptoms, the placebo plus SDT cohort in the PIONEER study demonstrated an least squares (LS) mean (SE) change from baseline in the ISM-SAF TSS of -9.15 (2.01) at Week 24. Only 9.9% of patients in the placebo plus SDT group achieved a $\geq 50\%$ reduction in TSS and 29.6% achieved a $\geq 30\%$ reduction. These results indicate that while SDT provides some relief, it results in a plateau of improvement after initial reduction, leaving a portion of patients inadequately controlled.⁴

The SUMMIT trial (evaluating bezuclastinib) reported a 18% mean improvement in the Mastocytosis Symptom Severity Daily Diary (MS2D2) TSS for its placebo plus SDT cohort at Week 12.³⁰ Additionally, the HARBOR trial (elenestinib) showed a mean TSS change from baseline of -22.2 in its placebo plus SDT group at Week 12.³¹ Meanwhile, the AB06006 trial (masitinib) used the 4R75% cumulative response (measuring pruritus, flushes, depression, or asthenia) as a primary endpoint, noting that while SDT provided some relief, it was not statistically superior to the active treatment in severe baseline symptoms.³²

Efficacy related to mast cell burden highlights that SDT in PIONEER had minimal-to-no impact on the biological drivers of the disease. Specifically, 0% of patients in the PIONEER SDT arm achieved a $\geq 50\%$ reduction in serum tryptase, with the group actually experiencing a mean increase of 9.65 ng/mL. Furthermore, only 6.3% reached a $\geq 50\%$ reduction in *KIT D816V* MAF and while 22.8% showed a $\geq 50\%$ reduction in bone marrow mast cell aggregates, the overall mean change was a 0.4% increase.^{2,4} This biological stagnation was consistently observed across other trial placebo-treated patients receiving SDT with minimal mean tryptase increases (HARBOR and AB06006) and a 0% response rate for $\geq 50\%$ tryptase reduction (SUMMIT).³⁰⁻³²

The safety profile of the SDT cohort in PIONEER revealed a high incidence of AEs, with 93.0% of participants experiencing at least one AE. Serious AEs (SAEs) occurred in 11.3% of the SDT group and Grade ≥ 3 AEs were reported in 21.1%. The

most common AEs in the SDT arm included headache (19.7%) and nausea (16.9%). In terms of tolerability, 1.4% of SDT patients permanently discontinued treatment due to AEs.^{2,4} Safety results from other trials showed similar burdens for the placebo +SDT arms. For instance, the AB06006 trial reported that 100% of patients in the placebo arm experienced AEs, with severe AEs in 35% of participants.³² In the SUMMIT trial, TEAEs were generally low-grade, though one patient in the placebo group suffered an acute myocardial infarction.³⁰

Regarding the inclusion of treatments within the PIONEER study, SDT treatments were comprised of several agents identified as potential comparators in the SLR. The included treatments consisted of H1-antihistamines (e.g., cetirizine), H2-antihistamines (e.g., cimetidine), PPIs (e.g., omeprazole), leukotriene inhibitors (e.g., montelukast), corticosteroids (e.g., prednisolone), mast cell stabilisers (e.g., sodium cromoglycate [nalcrom]), and anti-IgE antibodies (off-label omalizumab). Conversely, the therapies evaluated in the other trials listed in Table 7 (such as midostaurin, masitinib, bezuclastinib, elenestinib, nilotinib, lurrentelimab, cladribine and interferon- α) do not have marketing authorisation for ISM and were not included as components of the SDT regimen in PIONEER trial.⁴ While some of these (like TKIs) are used off-label in refractory cases, these are not currently NICE-recommended or part of standard NHS management for ISM.^{18,33,34}

Clinical effectiveness evidence

A 4. Priority. Table 7 shows defines the population PIONEER as: “Centrally confirmed WHO diagnosis of ISM with moderate to severe symptoms (ISM-SAF total symptom score $\geq$ 28) despite optimised symptom-directed therapy with $\geq$ 2 agents (H1/H2 blockers, leukotriene inhibitors, cromolyn sodium, corticosteroids or omalizumab).”

- a) Please make a comparison between this definition and all of the following: that in the marketing authorisation, the eligibility criteria for the SLR and those who would be eligible for avapritinib in English clinical practice.**

Please refer to Table 1 showing the definitions used in the marketing authorisation, SLR eligibility criteria (see Appendix B), and those eligible for avapritinib in English clinical practice, as well as their alignment with the PIONEER patient population.

Table 1: Patient population in PIONEER alignment

Patient population definition		Alignment with PIONEER patient population
Marketing authorisation	Adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment. ¹	• Yes, PIONEER trial is used as basis for the regulatory submission, albeit with more criteria under clinical trial conditions.
SLR eligibility criteria (see CS Appendix B)	Adult (age ≥18 years) patients with non-advanced systemic mastocytosis (non-AdvSM) which includes: • ISM • SSM	• Partially, scope in the PICO for the SLR are broader to avoid missing relevant sources in the literature sources.
NHS clinical practice	Patients with moderate to severe ISM eligible for avapritinib.	• In the UK, only patients categorised as moderate to severe (by clinician judgement according to ISM-SAF or other criteria) will be eligible for the treatment. For implementation in England, ISM-SAF will be made available for use by the company as it is the optimal measure of symptom burden in patients with ISM and will inform clinician judgement alongside quantitative measures of mast cell burden.⁵ • However, during validation of the economic model, NHS clinical experts highlighted that the PIONEER intention-to treat (ITT) population was considered to be representative and generalisable to UK patients eligible for avapritinib.^{5,24}

Abbreviations: AdvSM, advanced systemic mastocytosis; ISM, indolent systemic mastocytosis; ITT, intention-to-treat; NHS, National Health Service; PICO, Population-Intervention-Comparator-Outcome; SAF symptom assessment form; SLR, systematic literature review; SSM, smouldering systemic mastocytosis.

b) Please explain how any differences between the eligibility criteria in PIONEER and those patients eligible for avapritinib in English clinical practice might impact the generalisability of the trial to English clinical practice.

There are no discernible differences as English clinical practice will be directly informed by the anticipated marketing authorisation which is based on the pivotal PIONEER trial.^{1,4,5}

A 5. Priority. PIONEER required that patients had to be on ≥ 2 SDTs, and that:
“Participants received SDT according to treating physician's discretion.”
(page 44)

a) Please clarify if only patients who fulfil this criterion or whether patients in receipt of fewer SDTs would be eligible for avapritinib in UK clinical practice.

Patients with ISM will be eligible for avapritinib in UK clinical practice if they have moderate to severe symptoms inadequately controlled on symptomatic treatment.⁵ The marketing authorisation (expected in Q1 2026), while supported by the clinical evidence from the PIONEER trial, does not specify numbers of SDT treatments required.¹ Prior medications were defined as those that were both initiated and discontinued before the first exposure to the study drug. SDT medications could have been, and were for most patients, initiated prior to signing informed consent and nearly all patients were receiving ≥ 1 SDT medication upon enrollment, though all patients had previously received ≥ 2 SDT medications.⁴

b) Would UK clinicians generally regard treatment with ≥ 2 SDTs as “optimised therapy” in routine practice?

For routine NHS practice, a clinical expert confirmed that the use of at least 2 SDTs represents an optimally treated patient.²⁴ Some classes of available medications, including H1-/H2-antihistamines and leukotriene inhibitors are used most commonly. Mast cell stabilisers (sodium cromoglycate) are used off-label and may not be widely available. In clinic, most patients are managed with at least one medication from each of 2 or more classes of SDT which is representative of established clinical practice.²⁴

c) Please describe the implications for clinical effectiveness and cost-effectiveness of between patients in receipt of ≥ 2 SDTs and those in receipt of fewer SDTs, if this is the case in UK clinical practice.

As stated previously, UK clinical practice will be implemented according to avapritinib's marketing authorisation for moderate to severe patients inadequately controlled by symptomatic treatments (expected Q1 2026).¹ Moderate to severe patients with ISM are expected to have received multiple SDTs since diagnosis in NHS clinical practice (as per clinical expert feedback) which aligns with SDT (also termed BSC) in the PIONEER trial, therefore we foresee no differences in clinical or cost-effectiveness.^{5,24}

A 6. Priority. Regarding the generalisability of PIONEER to UK clinical practice:

Please provide baseline characteristics of all participants from Europe, and specifically from the United Kingdom if available.

The safety population for the European cohort consisted of [REDACTED] participants, while the UK-specific cohort comprised [REDACTED] participants. Both populations were predominantly female and under the age of [REDACTED]. While the UK cohort was [REDACTED] ethnically White, the European cohort also showed a high percentage of White participants ([REDACTED]), though [REDACTED] of the European data was recorded as 'Unknown'. A higher proportion of UK patients entered the study with an ECOG performance status of 2 ([REDACTED]) compared to the overall European population ([REDACTED]).³⁵ Table 2 summarises the key baseline characteristics to demonstrate the consistency between the regional and national data.

Table 2. Demographic and baseline characteristics of PIONEER participants in Europe and the UK

Characteristic	Europe overall (N=[REDACTED])	United Kingdom (N=[REDACTED])
Mean age (years)	[REDACTED]	[REDACTED]
Age group <65 years	[REDACTED]	[REDACTED]
Sex (female)	[REDACTED]	[REDACTED]
Race (white)	[REDACTED]	[REDACTED]
Mean BMI (kg/m ²)	[REDACTED]	[REDACTED]
ECOG performance status 0	[REDACTED]	[REDACTED]
ECOG performance status 1	[REDACTED]	[REDACTED]
ECOG performance status 2	[REDACTED]	[REDACTED]

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; N, number of individuals in the analysis.

Source: Blueprint Medicines Corporation Additional Efficacy Data (2025).²⁸

a) Please also provide alongside this, any available baseline data on UK based patients.

The disease burden at baseline, as measured by tryptase levels and mast cell infiltration, was generally higher in the UK cohort compared to the broader European population. UK participants exhibited a slightly higher disease burden at baseline compared to the European average. This was evidenced by a higher mean *KIT D816V* mutation allele burden (██████ in the UK vs ██████ in Europe) and a higher median serum tryptase (██████ ng/mL vs ██████ ng/mL). These are regarded as key drivers of disease activity in ISM, and are likely to represent more severe patients compared to other clinical trial sites.³⁶⁻³⁸

The prevalence of WHO SM diagnostic criteria was similar across both groups. Minor criteria (CD25 expression) were present in ██████ of both the European and UK safety populations.³⁵ Table 3 summarises the key baseline disease data to demonstrate the consistency between the regional and national data.

Table 3. Disease-specific baseline characteristics of PIONEER participants in Europe and the UK

Characteristic	Europe overall (N=██████)	United Kingdom (N=██████)
Median serum tryptase (ng/mL)	██████	██████
Tryptase 20 ng/mL	██████	██████
Mean BM mast cells (%)	██████	██████
Mean <i>KIT D816V</i> MAF (ddPCR)	██████	██████
History of anaphylaxis	██████	██████
Prior cytoreductive therapy	██████	██████
Prior TKI therapy	██████	██████

Abbreviations: BM, bone marrow; ddPCR, droplet digital polymerase chain reaction; KIT, KIT proto-oncogene receptor tyrosine kinase; MAF, mutant allele fraction; N, number of individuals in the analysis; TKI, tyrosine kinase inhibitor. Source: Blueprint Medicines Corporation Additional Efficacy Data (2025).²⁸

b) Please provide auditable detailed information from clinical experts regarding the degree to which the PIONEER population is comparable to the population found in UK clinical practice.

As part of clinical expert engagement and validation of the economic model, NHS clinical experts agreed that the PIONEER trial population is comparable to the population encountered in UK clinical practice (see Appendix J: UK primary research report).⁵

A 7. Priority. PIONEER required that patients had to be on ≥ 2 SDTs, and that: “Participants received SDT according to treating physician's discretion.” (page 44).

- a) Please provide a table which includes a comparison between percentages of patients who received SDT with different therapies in the PIONEER trial and percentages of patients who received established clinical management with different therapies in UK clinical practice.**

The proportion of patients who received SDT with different therapies in the PIONEER trial was presented in Table 39 in CS.³⁹ In alignment, the SDT distribution in the UK clinical practice was presented in Table 6 in CS.⁵

The management of patients with ISM and the PIONEER clinical trial characteristics was validated by three UK clinical experts in terms of generalisability and therapies administered the target population.⁵ Please see Table 4 below for detailed comparisons. For more information on clinical engagement, please see Appendix J: Primary research report along with CS.

Table 4: Symptom-directed treatment basket

Comparator	% patients in avapritinib + SDT arm (PIONEER) ^{4,28}	% patients in placebo + SDT arm (PIONEER) ^{4,28}	% patients in SDT (UK clinical practice)	Justification
H1-blockers (average)	██████	██████	██████ usage on H1-blockers, includes desloratadine, fexofenadine, cetirizine and loratadine (See Table 55 in the CS).	- Validated by three UK clinical experts.⁵ - One clinical expert from secondary engagement also proposed that 90% usage of H1-blockers is, on average.
H2-blocker (cimetidine)	██████	██████	██████ usage on H2-blockers, commonly used famotidine, cimetidine, and nizatidine. - According to the follow-up clinical expert engagement, ranitidine was previously very commonly used but the discovery of NDMA in some formulations led to most patients discontinuing it around 2020.	- Ranitidine was included in the PIONEER but excluded from the analysis due to safety concerns.^{23,40} - The proportion of H2-blocker usage was validated by three UK clinical experts.⁵ - One clinical expert from secondary engagement proposed that 80-90% usage of H2-blockers. - Ranitidine is discontinued in the UK, and its market authorisation was suspended by the MHRA and EMA due to it associated safety risk.^{40,41}
PPI (omeprazole)	██████	██████	██████	- Validated by three UK clinical experts.⁵ - One clinical expert from secondary engagement proposed that 30-40% usage of PPI.
Leukotriene inhibitor (montelukast)	██████	██████	██████	- Validated by three UK clinical experts.⁵ - One clinical expert proposed that possibly around ██████ usage of montelukast, and from secondary engagement

Comparator	% patients in avapritinib + SDT arm (PIONEER) ^{4,28}	% patients in placebo + SDT arm (PIONEER) ^{4,28}	% patients in SDT (UK clinical practice)	Justification
				proposed less than 20% usage.
Corticosteroid (prednisolone)	██████	██████	██████	Agreed and validated by three UK clinical experts.⁵
Cromolyn sodium (nalcrom)	██████	██████	██████	- Validated by three UK clinical experts.⁵ - One clinical expert thought that Nalcrom possible have a usage of around ██████ and from secondary engagement, the clinical expert proposed ██████ usage.
Monoclonal antibody (omalizumab)	██████	██████	██████	One clinical expert thought ██████ usage is sound, one clinical expert was not sure, and another one thought ██████ usage seems too high, but did not provide a validated value.⁵
Loperamide	Not used in the PIONEER trial	Not used in the PIONEER trial	██████	Not included in the analysis, as loperamide was not included in the PIONEER.

Abbreviations: H1/H2, antihistamines; PPI, proton-pump inhibitors; SDT, symptom-directed therapy; TKIs, tyrosine kinase inhibitors.

Note:1) UK clinicians confirmed that TKIs are rarely used in practice due to limited supporting evidence, though some use in ISM does occur, but not as part of SDT.⁵ 2) The average of H1-blockers used in PIONEER including desloratadine, fexofenadine, cetirizine, loratadine.

Table 5: H2-blockers included in the updated model

H1-blockers	Dose per syringe/ tablet (mg or mg/ml)	Units per package	Recommended dose per administration	Price per pack	Source
Famotidine	20 mg	28	20 mg	£2.49	BNF 2025,Part VIIIA Category M
Cimetidine	400 mg	60	400 mg	£4.52	eMIT 2023-25 (DCD042)
Nizatidine	150 mg	30	150 mg	£15.89	eMIT 2024/25 (DAE010)
Averages	NA	NA	190 mg	£7.63	Calculated

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; NA, not applicable.

Source: eMIT database.⁵ British National Formula.⁴²

b) Please describe any differences between SDT in the trial and treatments given in UK clinical practice to those eligible for avapritinib.

In both the PIONEER trial and UK practice, SDT is based on anti-mediator therapy and supportive care rather than disease-modifying agents. Almost of patients in the PIONEER trial received H1-blockers (97-100%), and around two-thirds of the patients in the PIONEER received an H2-blocker (66-69%). This aligns with UK practice where H1- and/or H2-antihistamines are used for initial symptom treatment of ISM.^{15,43}

Ranitidine was included in the PIONEER protocol but excluded from the analysis due to its market authorisation discontinuation in the UK (and the EU).^{40,41} Ranitidine was previously very commonly used in the UK clinical practice, but it had been recalled and withdrawn by manufacturers since 2020/2021 due to a substance linked to cancer risk.⁴⁰ Therefore, the main H2-blocker used in the analysis remained cimetidine.

In the current base case, only cimetidine was included as the primary H2-blocker agent (see CS CEM and Section B3.6.1.1). From the follow-up engagement with UK clinical experts confirmed famotidine is also commonly used in the NHS, with nizatidine also available though less common. The updated model has included these two additional medicines into the analysis.²⁴ Table 5 summarises a blended basket of H2-blockers included in the updated analysis. PPIs (omeprazole), montelukast, short courses of corticosteroids and sodium cromoglicate used in the PIONEER are consistent with UK practice.

Loperamide is available in the UK and is widely used for symptomatic treatment of acute diarrhoea. However, loperamide was not captured as part of the SDT basket in the PIONEER and no data are available on its use, impact on symptoms or health-related quality of life (HRQoL) in the trial population. Loperamide inclusion in the model would require additional assumptions regarding uptake and treatment effect that are not supported by robust evidence. The pack price of loperamide for a 2mg tablet listed on the BNF is £2.12, with 10-15% patients potentially eligible for this therapy.⁵ Consequently, any associated drug acquisition costs would have a minimal

impact on incremental costs and the overall cost-effectiveness results. For these reasons, loperamide was excluded from the SDT basket in the economic analysis.

The key difference in drug administration is related to off-label disease-directed TKIs which are used in the UK clinical practice alongside SDT but constitute an exclusion criteria in the PIONEER trial.^{5,23} As per validation from three UK clinical experts, TKI usage is uncommon in moderate to severe patients with ISM and a very small number of patients with uncontrolled disease may benefit from the treatment of TKIs as part of overall management alongside SDT.⁵

Overall, SDT in the PIONEER trial is representative of UK symptomatic management in terms of anti-mediator and supportive therapy.^{2,5,24} Rare administration of TKIs was noted by UK and Dutch clinical experts and guidance, but this off-label (or under clinical trial conditions) and is not part of the tailored SDT-based management of patients with ISM.^{5,18,44}

c) Please explain how these differences might impact the relative efficacy, safety and cost-effectiveness of avapritinib as it would be administered in UK clinical practice.

As noted in the previous part, client experts viewed the PIONEER trial as representative and generalisable to NHS clinical practice in terms of SDT-based management.^{2,5,24}

As a result, we foresee no difference with regards to clinical efficacy and safety despite experts noting a small proportion of patients [REDACTED] receiving off-label TKIs in addition to SDT. While we have presented scenarios for TKI usage in the cost-effectiveness modelling (see submitted CEM model and CS Section 3.11.3 Scenario analysis), there is no discernible difference in SDT-based management in the PIONEER trial and the UK clinical practice.^{5,24,39}

A 8. Priority. Table 31 in the CS shows that two patients randomised to avapritinib did not receive SDT and that 16 patients received only one class of SDT at baseline, despite the eligibility criterion of ≥ 2 SDTs.

a) Please explain how those patients were eligible for the study.

To clarify all patients enrolled in the PIONEER trial for either avapritinib or placebo treatments were treated with at least 2 current or prior SDT medications as per study eligibility criteria [see CS Section B2.4.3.1] and PIONEER clinical study report.⁴ This means that ≥ 2 SDT medications may have been administered prior to baseline measurements hence the figures reported in Table 31 of the CS.

b) Please provide change from baseline in SDT use for the placebo arm of PIONEER.

In addition to the effect on SDT medication usage at 24 weeks summarised in CS Section 2.7.6, Table 6 (see below) presents the change from baseline in SDT use for the placebo arm of PIONEER Part 2 at 24 weeks.³⁵ For the placebo arm, SDT medication usage is largely unchanged from baseline mean of [REDACTED] at 24 weeks. This equates to a mean change from baseline of [REDACTED].³⁵

Table 6: PIONEER Part 2 Change from baseline in SDT use

Parameter	Part 2 ITT population	
	Placebo (N=71)	Avapritinib 25 mg (N=141)
Baseline		
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]
C7D1	[REDACTED]	[REDACTED]
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]
C7D1 (24 weeks) change from baseline		
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]

Abbreviations: C, cycle; D, day; ITT, intention-to-treat; SD, standard deviation; SDT, symptom-directed therapy.

Note: Concomitant SDT medications are all medications used to manage symptoms of SM and taken at any time from first dose date of study drug to last dose date of study drug + 30 days. Baseline SDT is the number of SDT taken on C1D1. SDT at cycle 1 is number of SDT taken during C1D2 to C1D28. SDT at cycle x is number of SDT taken during cycle x, CxD1-CxD28, x=2,3,...etc.

Source: Blueprint Medicines PIONEER Part 2 Additional Efficacy Data on file (2025).³⁵

A 9. Priority. The CS states that: “The 100 mg dose demonstrated the fastest symptom reduction at Week 12, but plateaued thereafter. By Week 24, the 25 mg and 50 mg doses achieved comparable reductions. Based on Part 1 results, 25 mg avapritinib once daily was selected as the RP2D for subsequent study parts” (page 54). Please provide further justification for

selecting the 25 mg avapritinib dose for comparison with placebo in Part 2, rather than the 50 mg dose. To support assessment of dose selection, please provide:

- a) Any quantitative comparison of efficacy outcomes between the 25 mg and 50 mg dose groups in Part 1.**

In Part 1 of the PIONEER study, participants were randomised to receive placebo or avapritinib at doses of 25 mg, 50 mg or 100 mg once daily. Patients who received avapritinib 25 mg and 50 mg demonstrated that while higher doses showed slightly greater reductions in some objective biomarkers compared to placebo, TSS reduction was comparable by the 24 week analysis.⁴

Table 7 summarises the quantitative efficacy data from Part 1 comparing these two doses:

Table 7. Quantitative comparison of efficacy outcomes in PIONEER Part 1

Efficacy parameter	Avapritinib 25 mg (N=10)	Avapritinib 50 mg (N=10)
Mean change in TSS at Week 12 (C4D1)	██████	██████
Mean change in TSS at Week 24 (C7D1)	██████	██████
50% reduction in serum tryptase (Week 24)	████	████
50% reduction in <i>KIT D816V</i> MAF (Week 24)	████	████
50% reduction in BM mast cells (Week 24)	████	████
Mean % change in serum tryptase (Week 12)	████████	████████
Mean % change in BM mast cells (Week 12)	██████	██████

Abbreviations: BM, bone marrow; C4D1, Cycle 4 Day 1; C7D1, Cycle 7 Day 1; KIT, KIT proto-oncogene receptor tyrosine kinase; MAF, mutant allele fraction; mg, milligram; N, number of individuals in the analysis; TSS, Total Symptom Score

Source: Blueprint Medicines Corporation Clinical Study Report (2022).⁴

- b) Any rationale for deprioritising the 50 mg dose, particularly if it demonstrated comparable or greater early symptom reduction.**

The decision to select 25 mg once daily as the RP2D rather than 50 mg once daily was based on an integrated assessment of benefit-risk, safety and the chronic nature of ISM.

The 25 mg cohort demonstrated exceptional safety that was similar to placebo. During Part 1, the 25 mg group experienced no Grade 3 or greater AEs, no dose modifications and no early discontinuations due to AEs. In contrast, one patient in the 50 mg group discontinued treatment due to an AE.⁴

Further, unlike AdvSM, which is malignant and fatal, ISM is a non-malignant condition where people with the disease typically have a preserved life expectancy but suffer from lifelong, debilitating symptoms. Consequently, the benefit-risk assessment favoured the most well-tolerated, lowest effective dose to ensure patients could remain on therapy long-term.⁴

Although the 100 mg dose demonstrated the fastest initial symptom reduction, it plateaued after Week 12. By Week 24, the 25 mg and 50 mg doses achieved comparable reductions in TSS, suggesting that the lower dose was sufficient to achieve substantial clinical benefit without the potential for dose-related toxicities.⁴

The primary treatment goal in ISM is the reduction of symptom burden and improvement in QoL. Since 25 mg once daily effectively reduced both symptoms and all objective measures of mast cell burden while maintaining a superior safety profile, it was considered the most appropriate dose for comparison with placebo in the pivotal Part 2 of the study.⁴

A 10. Priority. The CS states that [REDACTED] participants underwent dose escalation in Part 3 of PIONEER, [REDACTED] of whom started on 25 mg.

a) Please clarify what the starting dose of the patients who did not start on 25 mg was.

For patients who experienced dose escalation of avapritinib ([REDACTED]) as of the latest DCO, the original starting doses of the patients who did not start on 25 mg in Part 1 were 50 mg ([REDACTED]), and 100 mg ([REDACTED]). Patients on 50 mg or 100 mg avapritinib in

Part 1 who rolled over to Part 3 were reduced to 25 mg (prior to any protocol-defined dose escalation).²⁸

b) Given that 50 mg is not included in the marketing authorisation, and NICE cannot make a decision outside of the marketing authorisation, please present the results for Part 3 excluding patients who experienced dose escalation.

For patients who dose escalated from 25 mg to 50 mg avapritinib (■■■■■), the original starting doses in Part 1/Part 2/Part 3 were 25 mg (■■■■■), 50 mg (■■■■■), and 100 mg (■■■■■). Patients on 50 mg or 100 mg avapritinib in Part 1 who rolled over to Part 3 were reduced to 25 mg (prior to any protocol-defined dose escalation).²⁸

With regards to patients from Part 3 who maintained their 25 mg dose up to 3 years (latest data cutoff [DCO]), the efficacy results are presented in the below tables for the key endpoints of the PIONEER trial. These results specifically exclude patients who experienced a protocol-defined dose escalation (see Appendix L for these patients not covered by marketing authorisation).²⁸ Also, regarding the results presented below, the data summarised from the tables from the patient population group treated with avapritinib (all starting doses) who maintained a 25 mg dose.

In the ITT population (all randomised participants), avapritinib treatment demonstrated substantial and sustained reductions in ISM-related symptom severity throughout 3 years of treatment. Mean (SD) reductions from baseline of ■■■■■ points in TSS were observed at 1 year of treatment with avapritinib, with sustained reductions maintained through 2 years (■■■■■ points) and 3 years (■■■■■ points) of treatment (Table 8). These reductions were consistent regardless of participants' starting dose of avapritinib. Sensitivity analysis of the per-protocol ([PP]; participants without major protocol deviations) population showed comparable results to the ITT population, with mean (SD) reductions from baseline of ■■■■■ points in TSS observed at 1 year of treatment with avapritinib, with further sustained reductions observed at 2 years (■■■■■ points) and 3 years (■■■■■ points) of treatment (Table 8).²⁸

Long-term treatment with avapritinib demonstrated sustained clinically meaningful response rates, with consistent proportions of participants achieving both moderate ($\geq 30\%$) and substantial ($\geq 50\%$) reductions in symptom burden at 1 year from baseline across different analysis populations (Table 8).²⁸

In the ITT population (all starting doses), [REDACTED] of participants achieved a $\geq 30\%$ reduction in TSS by 1 year from baseline, while [REDACTED] of participants achieved a $\geq 50\%$ reduction in TSS. These response rates were consistent regardless of participants' starting dose of avapritinib. The PP population showed comparable response rates to the ITT population, where [REDACTED] of participants had a $\geq 30\%$ reduction in TSS and [REDACTED] of participants had a $\geq 50\%$ reduction in TSS at 1 year from baseline.²⁸

In both ITT and PP populations (regardless of starting dose), in participants who maintained a 25-mg dose of avapritinib as of the time of the data cut, comparable reductions in TSS were demonstrated at 1, 2 and 3 years of treatment, with similar proportions of participants exhibited $\geq 30\%$ and $\geq 50\%$ reductions in TSS.²⁸

Table 8: PIONEER Part 3 Change in ISM-SAF TSS from baseline up to 3 years avapritinib

Parameter	Part 3 ITT population		PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Baseline (i.e. start of treatment)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
TSS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
C13D1 (~1 year from baseline)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
TSS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
TSS change from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent TSS change from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Parameter	Part 3 ITT population		PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N				
TSS, mean (SD)				
TSS change from baseline, mean (SD)				
Percent TSS change from baseline, mean (SD)				
C40D1 (~3 years from baseline)				
N				
TSS, mean (SD)				
TSS change from baseline, mean (SD)				
Percent TSS change from baseline, mean (SD)				
Patients with ≥30% or ≥50% reductions in TSS				
Proportion with ≥30% reduction in TSS by 1 year from baseline, n (%) [95% CI]				
Proportion with ≥50% reduction in TSS by 1 year from baseline, n (%) [95% CI]				

Abbreviations: CxDx, Cycle x, Day x; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; SD, standard deviation; TSS, total symptom score.

Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Data from 25 mg dose maintained patients is presented above with data from dose escalated (to 50 mg) group excluded.

Source: Blueprint Medicines Corporation Clinical Study Report (2025).²⁸

Reductions in serum tryptase level relative to baseline were demonstrated with long-term avapritinib treatment up to 3 years.²⁸ In patients treated with avapritinib (all starting doses and 25 mg dose maintained), a reduction in median percent concentration change from baseline of was reported in the ITT population at 1 year of treatment. This reduction from baseline was maintained as of 2 years

(██████) and 3 years (██████) of treatment (Table 9). These findings were observed irrespective of participants' starting dose of avapritinib.²⁸ In the PP population, median percent reductions from baseline of ██████ were observed at 1 year of treatment, maintained at 2 years (██████) and 3 years (██████) of treatment, with these findings observed irrespective of participants' starting dose of avapritinib (Table 9).²⁸

Table 9: PIONEER Part 3 Change in serum tryptase from baseline up to 3 years avapritinib

Parameter	Part 3 ITT population		PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Baseline (i.e. start of treatment)				
N	██████	██████	██████	██████
Concentration, median, ng/mL (range)	██████ ██████	██████ ██████	██████ ██████	██████ ██████
C13D1 (~1 year from baseline)				
N	██████	██████	██████	██████
Concentration, median, ng/mL (range)	██████ ██████	██████ ██████	██████ ██████	██████ ██████
Change in concentration from baseline, median, ng/mL (range)	██████ ██████	██████ ██████	██████ ██████	██████ ██████
Percent change in concentration from baseline, median (range)	██████ ██████	██████ ██████	██████ ██████	██████ ██████

	Part 3 ITT population		PP population	
Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N	████	████	████	████
Concentration, median, ng/mL (range)	████ █	████ █	████	████ █
Change in concentration from baseline, median, ng/mL (range)	████ █	████ █	████ █	████ █
Percent change in concentration from baseline, median (range)	████ █	████ █	████ █	████ █
C40D1 (~3 years from baseline)				
N	████	████	████	████
Concentration, median, ng/mL (range)	████ █	████ █	████	████ █
Change in concentration from baseline, median, ng/mL (range)	████ █	████ █	████ █	████ █
Percent change in concentration from baseline, median (range)	████ █	████ █	████ █	████ █

Abbreviations: CxDx, Cycle x, Day x; ITT, intention-to-treat; PP, per-protocol.

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Data from 25 mg dose maintained patients is presented above with data from dose escalated (to 50 mg) group excluded.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

For another objective measure of mast cell burden, *KIT D816V* variant allele fraction (VAF) also showed a consistent long-term improvement with avapritinib treatment up to 3 years.²⁸ In patients treated with avapritinib (all starting doses and 25 mg dose maintained), a reduction in median percent change in *KIT D816V* VAF at 1 year avapritinib treatment from baseline of █████ and █████ was reported in the ITT and PP populations, respectively. This reduction from baseline was maintained at 2 years (████) and 3 years (████) of avapritinib treatment (ITT/PP

population respectively; Table 10). These findings were observed irrespective of participants' starting dose of avapritinib.²⁸

Table 10: PIONEER Part 3 Change in *KIT* D816V VAF from baseline up to 3 years avapritinib

Parameter	Part 3 ITT population		PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Baseline (i.e. start of treatment)				
N	████	████	████	████
<i>KIT</i> D816V VAF, median (range)	██████████	██████████	██████████	██████████
C13D1 (~1 year from baseline)				
N	████	████	████	████
<i>KIT</i> D816V VAF, median (range)	██████████	██████████	██████████	██████████
Change in <i>KIT</i> D816V VAF from baseline, median (range)	██████████	██████████	██████████	██████████
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)	██████████	██████████	██████████	██████████

Parameter	Part 3 ITT population		PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N	■	■	■	■
<i>KIT</i> D816V VAF, median (range)	■	■	■	■
Change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
C40D1 (~3 years from baseline)				
N	■	■	■	■
<i>KIT</i> D816V VAF, median (range)	■	■	■	■
Change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■

Abbreviations: CxDx, Cycle x, Day x; ITT, intention-to-treat; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PP, per-protocol; VAF, variant allele frequency.

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Data from 25 mg dose maintained patients is presented above with data from dose escalated (to 50 mg) group excluded.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

For HRQoL efficacy results up to 3 years of avapritinib treatment, refer to Table 11 (MC-QoL), Table 12 (EQ-5D-5L), Table 13 (SF-12), and Table 14 (PGIS and PGIC) for ITT and PP population patients who maintained the 25 mg dose during PIONEER Part 3.²⁸

Mean MC-QoL total score demonstrated a consistent reduction after up to 3 years compared to baseline regardless of population (ITT or PP) or starting dose (Table 11). At 1 year of avapritinib treatment, MC-QoL was reduced by ■ (ITT population) or ■ (PP population). This treatment effect was

maintained after 2 years (██████████ points) and 3 years (██████████ points). Participants who maintained a 25 mg dose of avapritinib across both ITT and PP populations showed comparable reductions in mean MC-QoL total score from baseline to 1, 2 and 3 years of post-baseline follow-up as the overall populations (including dose escalated patients).²⁸

Table 11: PIONEER Part 3 Change in MC-QoL total score from baseline up to 3 years avapritinib

Parameter	Part 3 ITT population		Part 3 PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Baseline (i.e. start of treatment)				
N	████	████	████	████
MC-QoL total score, mean (SD)	██████████	██████████	██████████	██████████
C13D1 (~1 year from baseline)				
N	████	████	████	████
MC-QoL total score, mean (SD)	██████████	██████████	██████████	██████████
Change in MC-QoL total score from baseline, mean (SD)	██████████ T	██████████ T	██████████ T	██████████ T
Percent change in MC-QoL total score from baseline, mean (SD)	██████████ T	██████████ T	██████████ T	██████████ T
C25D1 (~2 years from baseline)				
N	████	████	████	████
MC-QoL score,	██████████	██████████	██████████	██████████

Parameter	Part 3 ITT population		Part 3 PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
mean (SD)				
Change in MC-QoL total score from baseline, mean (SD)				
Percent change in MC-QoL total score from baseline, mean (SD)				
C40D1 (~3 years from baseline)				
N				
MC-QoL score, mean (SD)				
Change in MC-QoL total score from baseline, mean (SD)				
Percent change in MC-QoL total score from baseline, mean (SD)				

Abbreviations: CxDx, Cycle x, Day x; MC-QoL, ITT, intention-to-treat; Mastocytosis Quality of Life; PP, per-protocol; SD, standard deviation.

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Data from 25 mg dose maintained patients is presented above with data from dose escalated (to 50 mg) group excluded.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

As well as MC-QoL, increases in mean EQ-5D-5L scores from baseline to 1 year (██████), 2 years (██████) and 3 years (██████) of avapritinib treatment in the ITT population were observed, indicating sustained improvements in HRQoL.

Improvements in mean EQ-5D-5L scores were consistent in the PP population, with increases of ██████ at 1 year, ██████ at 2 years, and ██████ at 3 years (Table 12).

These improvements were consistent regardless of participants' starting dose of avapritinib those maintaining the 25 mg dose in PIONEER Part 3.²⁸

Table 12: PIONEER Part 3 Change in EQ-5D-5L scores from baseline up to 3 years avapritinib

Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Baseline (i.e. start of treatment)				
N	████	████	████	████
EQ-5D-5L index value, mean (SD)	██████	██████	██████	██████
C13D1 (~1 year from baseline)				
N	████	████	████	████
EQ-5D-5L index value, mean (SD)	██████	██████	██████	██████
Change in EQ-5D-5L index value from baseline, mean (SD)	██████	██████	██████	██████
Percent change in EQ-5D-5L index value from baseline, mean (SD)	██████	██████	██████	██████

Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N	■	■	■	■
EQ-5D-5L index value, mean (SD)	■	■	■	■
Change in EQ-5D-5L index value from baseline, mean (SD)	■	■	■	■
Percent change in EQ-5D-5L index value from baseline, mean (SD)	■	■	■	■
C40D1 (~3 years from baseline)				
N	■	■	■	■
EQ-5D-5L index value, mean (SD)	■	■	■	■
Change in EQ-5D-5L index value from baseline, mean (SD)	■	■	■	■
Percent change in EQ-5D-5L index value from baseline, mean (SD)	■	■	■	■

Abbreviations: CxDx, Cycle x, Day x; EQ-5D-5L, EuroQoL 5-Dimension 5-Level questionnaire; ITT, intention-to-treat; PP, per-protocol; SD, standard deviation.

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. Data from 25 mg dose maintained patients is presented above with data from dose escalated (to 50 mg) group excluded.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

Participants in both the ITT and PP populations (excluding dose escalated patients in PIONEER Part 3) demonstrated sustained improvements in HRQoL as measured by the SF-12 Physical Component Score (PCS) and Mental Component Score (MCS) throughout the 3 year treatment period (Table 13).²⁸

In the ITT population, mean SF-12 PCS scores increased from baseline by ■ points at 1 year, ■ points at 2 years and ■ points at 3 years for participants receiving all starting doses. Corresponding improvements in mean SF-12 MCS scores were ■ points at 1 year, ■ points at 2 years and ■ points at 3 years. The PP population demonstrated comparable improvements in both PCS and MCS. Mean SF-12 PCS scores increased from baseline by ■ points at 1 year, ■ points at 2 years and ■ points at 3 years for participants receiving all

starting doses. Mean SF-12 MCS scores showed improvements of [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years.²⁸

These improvements in SF-12 scores were consistent regardless of participants' starting dose of avapritinib and were maintained across both analysis populations.

Table 13: PIONEER Part 3 Change in SF-12 physical and mental component scores from baseline up to 3 years avapritinib

Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Physical component summary score				
<i>Baseline (i.e. start of treatment)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SF-12 PCSS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<i>C13D1 (~1 year from baseline)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SF-12 PCSS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in SF-12 PCSS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent change in SF-12 PCSS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N	■	■	■	■
SF-12 PCSS, mean (SD)	■	■	■	■
Change in SF-12 PCSS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 PCSS from baseline, mean (SD)	■	■	■	■
C40D1 (~3 years from baseline)				
N	■	■	■	■
SF-12 PCSS, mean (SD)	■	■	■	■
Change in SF-12 PCSS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 PCSS from baseline, mean (SD)	■	■	■	■
Mental component summary score--				
Baseline (i.e. start of treatment)				
N	■	■	■	■
SF-12 MCSS, mean (SD)	■	■	■	■
C13D1 (~1 year from baseline)				
N	■	■	■	■
SF-12 MCSS, mean (SD)	■	■	■	■
Change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■

Parameter	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
C25D1 (~2 years from baseline)				
N	■	■	■	■
SF-12 MCSS, mean (SD)	■	■	■	■
Change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■
C40D1 (~3 years from baseline)				
N	■	■	■	■
SF-12 MCSS, mean (SD)	■	■	■	■
Change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCSS from baseline, mean (SD)	■	■	■	■

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.

Abbreviations: C, Cycle; D, Day; ITT, intention-to-treat; MCS, mental component summary score; PCS, physical component summary score; PP, per-protocol; SD, standard deviation; SF-12, 12-Item Short Form Health Survey.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

For PGIS and PGIC measures, Table 14 presents data up to 3 years of avapritinib treatment in patients maintaining a 25 mg dose.²⁸

In the ITT population, consistent decreases in mean PGIS score were observed from baseline through 3 years of avapritinib treatment, suggesting sustained reductions in symptom severity.^{28,45} For participants receiving all starting doses, mean PGIS scores decreased from baseline by ■ points at 1 year, ■ points at 2 years and ■ points at 3 years. The PP population demonstrated comparable reductions in PGIS scores, with mean decreases from baseline of ■ points at 1 year, ■ points at 2 years and ■ points at 3 years for participants receiving all starting doses. Aligned with PGIS findings, participants in both the ITT and PP populations reported meaningful improvements in their symptom severity whilst on treatment.²⁸

In the ITT population, mean PGIC scores of approximately [REDACTED] points were observed at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years post-baseline for participants receiving all starting doses. The PP population showed similar PGIC scores, with mean values of [REDACTED] points at 1 year, [REDACTED] points at 2 years and [REDACTED] points at 3 years for participants receiving all starting doses (Table 14).²⁸

These reductions in PGIS and PGIC were consistent regardless of participants' starting dose of avapritinib and were maintained across both analysis populations throughout the 3-year treatment period.²⁸

Table 14: PIONEER Part 3 PGIS and PGIC for patients treated with avapritinib (up to years)

Parameter	Part 3 ITT population		Part 3 PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
PGIS				
<i>Baseline (i.e. start of treatment)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PGIS score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<i>C13D1 (~1 year from baseline)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PGIS score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in PGIS score from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<i>C25D1 (~2 years from baseline)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PGIS score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in PGIS score from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<i>C40D1 (~3 years from baseline)</i>				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PGIS score, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Parameter	Part 3 ITT population		Part 3 PP population	
	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained	Avapritinib, 25-mg starting dose and dose maintained	Avapritinib, all starting doses and 25-mg dose maintained
Change in PGIS score from baseline, mean (SD)				
PGIC (7-point scale)				
C13D1 (~1 year from baseline)				
N				
PGIC score, mean (SD)				
C25D1 (~2 years from baseline)				
N				
PGIC score, mean (SD)				
C40D1 (~3 years from baseline)				
N				
PGIC score, mean (SD)				

Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The PGIS scale ranges from 0 (none) to 4 (very severe). The PGIC scale ranges from 1 (very much worse) to 7 (very much better), with a score of 4 indicating no change and 5 indicating moderately better.

Abbreviations: C, Cycle; D, Day; ITT, intention-to-treat; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Symptom Severity; PP, per-protocol; SD, standard deviation.

Source: Blueprint Medicines Corporation PIONEER Clinical Study Report (2025).²⁸

A 11. Priority. Relating to discontinuation of avapritinib:

- a) Please provide full details of the number of patients who discontinued avapritinib, the reasons (including adverse events or disease progression) and the timing.

Across the safety population (N=246), a total of █ patients discontinued avapritinib treatment during the follow-up period, including █ participant who completed Part 2 assessments but chose not to roll over to the Part 3 long-term extension. The primary reasons for avapritinib discontinuation included withdrawal by subject (█), AEs (█), physician decisions (█), and disease progression (█) with the full summary of the reasons for discontinuation and variable duration of treatment before discontinuation are presented in Table 15.³⁵

Table 15. Summary of reasons for discontinuation of avapritinib treatment in PIONEER study Parts 1/2/3

Reason for discontinuation	Number of participants	Duration of avapritinib treatment before discontinuation, mean (range) months
Withdrawal by subject	█	█
AE	█	█
Physician decision	█	█
Progressive disease	█	█
Non-compliance	█	█
Lost to follow-up	█	█
Death	█	█
Pregnancy	█	█
Other	█	█
Total discontinued	█	

Abbreviations: AE, adverse event. Source: Blueprint Medicines Corporation PIONEER Additional Efficacy Data (2025).³⁵

- b) Please provide an analysis of time to treatment discontinuation over the entire follow-up period, including Part 3 of PIONEER, which includes a Kaplan-Meier plot, an estimate of the median time to discontinuation, and the average rate of discontinuation.**

This analysis of time to treatment discontinuation (TTD) covers the entire follow-up period, including Part 3 of the PIONEER study (data cutoff date 21 February 2025). The median TTD for the overall population was █ months (█ CI: █). Across the treatment groups, median TTD ranged from █ to █ months in the PIONEER safety population (Table 17).³⁵

Table 16. Time to treatment discontinuation in PIONEER Safety Population

Treatment group	N	Events (%)	Median time to treatment discontinuation (months [95% CI])
Overall	█	█	█
Placebo to 25 mg	█	█	█
Avapritinib 25 to 25 mg	█	█	█
Avapritinib 50 to 25 mg	█	█	█
Avapritinib 100 to 25 mg	█	█	█

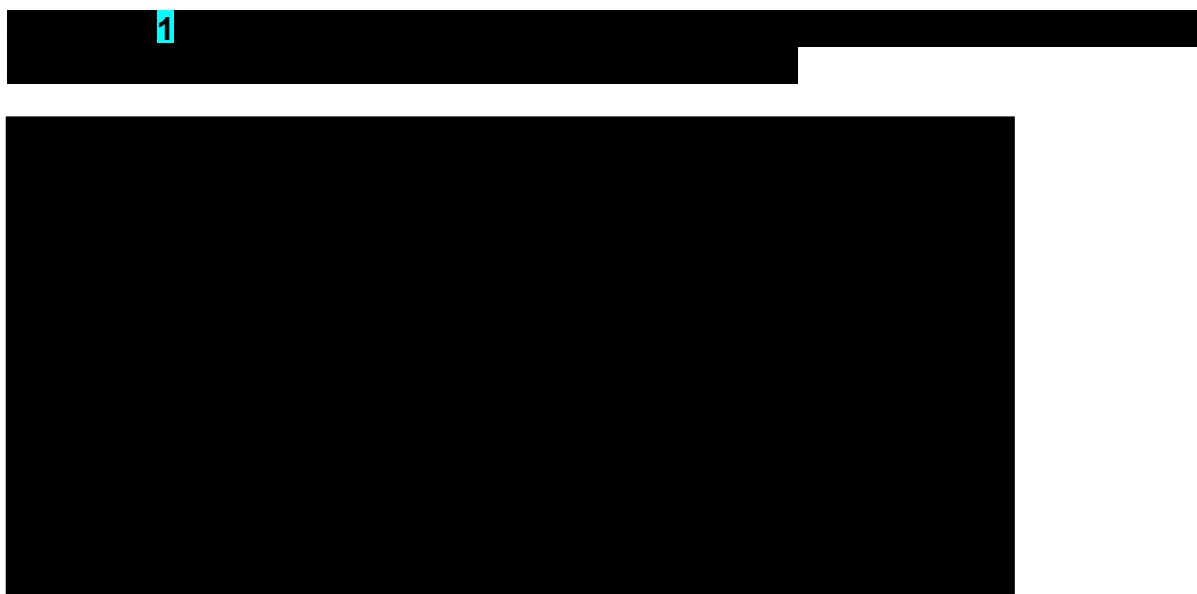
Abbreviation: CI, confidence interval

Source: Blueprint Medicines Corporation Additional Efficacy Data (2025).³⁵

The probability of remaining on treatment remained high throughout the first 3 years of the study, with a more pronounced decline observed after 60 months of follow-up:³⁵

- 12 months: [REDACTED] probability of remaining on treatment
- 24 months: [REDACTED] probability of remaining on treatment
- 36 months: [REDACTED] probability of remaining on treatment
- 48 Months: [REDACTED] probability of remaining on treatment
- 60 months: [REDACTED] probability of remaining on treatment

The Kaplan-Meier plot provided in Figure 1 illustrates the high retention rate on avapritinib, with the "Overall" curve (black line) maintaining a probability above [REDACTED] until approximately Month [REDACTED], before the final decline toward the median at [REDACTED] months.³⁵



Source: Blueprint Medicines Corporation Additional Efficacy Data (2025)²⁸

A 12. It states on page 61 of the CS when describing MC-QoL data that ‘A post-hoc sensitivity analysis excluding French translations (due to mistranslation issues) was consistent with the overall analysis’. To confirm consistency, please provide further details on this and describe the extent of these issues as well as providing the whole analysis results alongside those without the French translations

In PIONEER Part 2, HRQoL was assessed with the 27-item MC-QoL questionnaire at 24 weeks in placebo and avapritinib 25 mg treated patients (Table 18).^{4,35} Overall, a greater reduction in MC-QoL percentage change from baseline was observed in the full ITT population for avapritinib group ([REDACTED] vs placebo group [REDACTED]. Following the post-hoc sensitivity analysis (exclusion of French

mistranslations), MC-QoL was similarly affected by avapritinib treatment

██████████ compared to placebo control group ██████████. ³⁵

Table 17: PIONEER Part 2 MC-QoL change from baseline at 24 weeks

Parameter	Part 2 Full ITT population		Part 2 ITT population (removing patients affected by French mistranslation)	
	Placebo	Avapritinib	Placebo	Avapritinib
Baseline (i.e. start of treatment)				
N	████	████	████	████
Mean (SD)	██████████	██████████	██████████	██████████
MC-QoL total score at 24 weeks (C7D1)				
N	████	████	████	████
Mean (SD)	██████████	██████████	██████████	██████████
Median (Min, Max)	██████████	██████████	██████████	██████████
MC-QoL total score change from baseline				
N	████	████	████	████
Mean (SD)	██████████	██████████	██████████	██████████
Median (Min, Max)	██████████	██████████	██████████	██████████
MC-QoL Percentage change from baseline at 24 weeks				
N	████	████	████	████
Mean (SD)	██████████	██████████	██████████	██████████
Median (Min, Max)	██████████	██████████	██████████	██████████

Abbreviations: ITT, intention-to-treat; MC-QoL, Mastocytosis Quality of Life questionnaire; SD, standard deviation.

Source: Blueprint Medicines PIONEER Additional Efficacy Data on file (2025).³⁵

A 13. The CS appears to describe and prioritise results that are predominantly concerned with patient reporting of symptom burden but comparative data is limited on influence of intervention on altered pathogenesis or physiology such as mast cell burden. Please justify such an emphasis and provide further details if available on impact on disease progression or status.

In the clinical management of ISM, the primary treatment goal is the reduction of persistent, debilitating symptoms, and the improvement of social and physical functionality (via HRQoL measures).^{14,46} In alignment with the needs of patients, the PIONEER clinical trial's primary objective was the change in ISM-SAF TSS which has been accepted by regulatory agencies (FDA and EMA) and used as a basis for reimbursement approval.^{47,48} This primary endpoint allowed the sensitive and specific evaluation of the effects on symptom burden due to avapritinib therapy which reflects the unmet need in patients with ISM.⁴

Unlike advanced forms of the disease, ISM is characterised by a range of fluctuating symptoms characterised by MC infiltration in skin and at extracutaneous sites such as bone marrow, liver, spleen, lymph nodes, and GI.⁴⁹ These manifestations are part of broad, heterogeneous symptom profile which dominates day-to-day living with negative impacts on HRQoL and daily functioning.^{12,14,21,50} As described in CS Section 1.3.7.1, most patients with ISM (60-70%) are reported as having moderate to severe symptoms as per patient survey in the PRISM study.^{12,20,21} As such, the ISM-SAF was developed and rigorously validated with input from patients and regulatory authorities specifically to fill the gap in standardised symptom quantification for this population.⁸⁻¹⁰ As retention of social and role functionality is of paramount concern for patients, the TSS remains the most appropriate primary clinical measure for evaluating therapeutic effectiveness.⁸⁻¹⁰

While this emphasis on symptom reporting is necessitated by the primary clinical burden of ISM, the PIONEER trial results concurrently demonstrate that avapritinib has disease-modifying effects on causal underlying disease pathophysiology reducing objective disease burden and achieving sustained symptom control that current SDT cannot provide.⁴

Comparative data from PIONEER Part 2 demonstrate that avapritinib significantly reduces objective markers of mast cell burden at Week 24:⁴

- Serum tryptase: 53.9% of participants on avapritinib achieved a $\geq 50\%$ reduction, compared to 0.0% on placebo ($p < 0.0001$).

- *KIT D816V* allele burden: 67.8% of participants achieved a $\geq 50\%$ reduction in peripheral blood *KIT D816V* VAF or reached undetectable levels, vs 6.3% on placebo ($p < 0.0001$).
- Bone marrow mast cells: 52.8% of participants saw a $\geq 50\%$ reduction in bone marrow mast cells or total clearance of mast cell aggregates, compared to 22.8% on placebo ($p < 0.0001$).

In the PIONEER trial protocol, "SM clinical progression" is defined as the evolution of the disease into more advanced variants, such as smouldering systemic mastocytosis (SSM) or advanced systemic mastocytosis (AdvSM).⁴ Progression from ISM to advanced variants is an infrequent event in the natural history of the disease. The cumulative probability of such progression is reported at 1.7% at 5 to 10 years and 8.4% at 20 to 25 years.⁵¹ Long-term results from the Part 3 open-label extension support the rarity of these events. Of 246 participants who received avapritinib, only 1 participant (0.4%) discontinued treatment due to progressive disease as of the data cutoff 2 February 2025.³⁵ Further, high *KIT D816V* VAF ($\geq 6\%$ in peripheral blood) is a documented risk factor for progression to AdvSM. Therefore, the deep and sustained reductions in VAF observed with avapritinib suggest a potential for reducing the long-term risk of disease worsening (as shown in Table 10 for CQ A10).²⁸

Indirect treatment comparison (ITC)

A 14. Priority. No ITC was conducted, but the EAG understands that some comparator treatments, e.g. TKIs, were not included in PIONEER.

- Please consider the feasibility of ITCs or network meta-analysis (NMA) to compare avapritinib with those treatments.**
- Please conduct ITCs or and NMA for those treatments using the most appropriate methodology, considering the number of comparators and the nature of the evidence e.g. whether there are common comparators.**

Avapritinib is the only targeted treatment approved for ISM and the PIONEER trial already provides a direct comparison with the only established clinical management

(SDT). As such, the evidence base is best represented by the direct randomised controlled trial (RCT) data already provided. An ITC or NMA is not feasible/required because, in addition to avapritinib being the first and only therapy approved for adult patients with ISM, there is an absence of head-to-head trial data and other investigational trials utilise heterogeneous clinical endpoints and patient populations that cannot be reliably aligned for statistical comparison. Structural and clinical evidence limitations include:

- Part 2 of the PIONEER trial was a randomised, double-blind, placebo-controlled study, providing a high-level, "gold standard" comparison of avapritinib plus SDT versus placebo plus SDT. This trial design is considered the highest level of evidence for establishing the efficacy of avapritinib against current standard clinical management.^{2,52}
- Avapritinib is currently the first and only therapy approved for adult patients with ISM whose symptoms are inadequately controlled by symptomatic treatment. No other TKI treatment, including those used in AdvSM, such as midostaurin, has received marketing authorisation in the UK for ISM.^{15,53}
- The SLR identified other off-label TKIs currently under investigation (e.g., elenestininib, masitinib and bezucclastininib) which have been evaluated in separate RCTs. However, these trials utilised heterogeneous endpoints that cannot be statistically aligned. PIONEER utilised the ISM-SAF TSS, whereas the SUMMIT trial used the Mastocytosis Symptom Severity Daily Diary (MS2D2) and the AB06006 trial used a unique 4R75% cumulative response definition.^{2,30-32}
- While some TKIs like midostaurin or imatinib are occasionally used off-label, UK clinical experts have confirmed that such use is exceptionally rare and mostly unfunded in NHS clinical practice. In the PIONEER trial itself, only a very small proportion of participants (7.1% in the avapritinib arm and 5.6% in the placebo arm) had received any prior TKI therapy, reflecting its limited role as a comparator in this population.⁵

- The clinical SLR confirmed that there are no head-to-head trials comparing avapritinib with other targeted agents in ISM. Because all identified trials were placebo-controlled and utilised vastly different patient populations and assessment tools, any indirect comparison would be subject to large bias and uncertainty.
- The ITT population in PIONEER is considered highly generalisable to the UK patients eligible for avapritinib, whereas investigational data for other TKIs often target different severities or symptom profiles.⁵

Adverse events

A 15. Priority. Limited data are presented on anaphylaxis occurring in the PIONEER trial.

- a) Please provide the numbers of patients/events, and timing (by week and Part) of those events for both those randomised avapritinib and those randomised to placebo.**

During the course of PIONEER Part 2 (randomised avapritinib vs placebo for 24 weeks), the number of anaphylaxis events treated with epinephrine were recorded during screening (baseline) and throughout the study (24 weeks post-baseline).^{4,35} At baseline, [REDACTED] patients in the 25 mg avapritinib group and none in the placebo group had anaphylaxis that required epinephrine treatment. Post-baseline, [REDACTED] patients in the 25 mg avapritinib group and [REDACTED] in the placebo group had anaphylaxis that required epinephrine treatment.^{4,35}

It should be noted that the above results are for PIONEER Part 2 up to 24 weeks only, and the timing of the anaphylactic events was not captured for all patients across the multiple clinical trial sites.^{4,35}

- b) Please provide an estimate of the treatment effect (avapritinib versus placebo) on anaphylaxis.**

Exploratory analyses revealed a reduction of anaphylaxis frequency with avapritinib treatment, [REDACTED] of patients who had baseline anaphylaxis ([REDACTED]) experienced no post-baseline events during the 24-week treatment period, compared to all

placebo patients (■■■■) developing anaphylaxis only during treatment. With this small sample size of patients/anaphylactic events, it is difficult to infer treatment effect highlighting the need for further study in a real-world setting over longer periods of time.³⁵

Section B: Clarification on cost-effectiveness data

Population

B 1. Priority: The population in the company's economic model was informed by the per protocol population of PIONEER, including ISM patients with moderate to severe symptoms. Patients with dose escalation (daily dose of 50 mg) in PIONEER were excluded, i.e. the company's base-case analysis focused on patients treated with avapritinib at a daily dose of 25 mg versus SDT. Patient baseline characteristics in the company's base-case were informed by UK clinical input (starting age) and PIONEER (gender and weight).

a) Please comment on the generalisability of the patient baseline characteristics in CS Table 41 to UK clinical practice.

CS Table 41 summarises baseline characteristics from the PIONEER population used to inform the model. Overall, UK clinical experts considered the trial population to be broadly generalisable to UK clinical practice in terms of key demographic characteristics relevant to treatment and resource use, with one important adjustment relating to age.^{5,24} Age: UK clinical experts advised that ISM typically presents at an earlier age than the PIONEER baseline (mean age 51 years). To better reflect UK clinical practice, the model uses a starting age of 40 years, as validated in the clinical expert report.⁵

- Sex distribution: Follow-up expert engagement confirmed that the sex distribution in CS Table 41 is consistent with the ISM population seen in UK specialist practice.²⁴
- Body weight: Follow-up expert engagement also validated that the mean body weight reported in CS Table 41 is broadly representative of UK patients and appropriate for modelling purposes.²⁴

Taken together, the company considers CS Table 41 to be generally applicable to UK clinical practice for modelling, with the starting age adjusted to reflect UK expert opinion on age at onset. Remaining differences between trial and UK practice are

expected to reflect normal variation across countries and recruitment settings rather than systematic differences in disease management.⁵

b) Please justify why starting age informed by UK clinical input (40 years) was deemed more appropriate than age informed by PIONEER (51 years).

The clinical adjustment of the starting age (40 years) used in the model was informed and validated by three UK clinical experts, reflecting the burden of ISM, the full spectrum symptomatology and current disease management in NHS perspective. UK clinical experts indicated that ISM typically presents at an earlier age than observed in the PIONEER population (mean age 51 years), and that a plausible onset age is around 30-50 years. A starting age of 40 years was validated and therefore selected as a pragmatic assumption.⁵ Further details on this clinical opinion are provided in Q7 in Appendix J: Primary research report submitted along with CS.

c) Please justify which population from PIONEER (i.e. full ITT with or without dose escalation, or moderate to severe subgroup with or without dose escalation) was used to inform the PIONEER-based patient baseline characteristics as reported in CS Table 41.

In line with the anticipated SmPC, avapritinib at a daily dose of 25mg is indicated for the treatment of adults with moderate to severe ISM inadequately controlled with symptomatic treatment.¹ Three UK clinical experts have validated this clinical input.⁵ Thus, the primary base-case analysis considers moderate to severe ISM patients treated with avapritinib 25mg once daily without dose escalation, as this group best reflects the target population for the anticipated UK marketing authorisation.¹

Other subgroup populations are excluded from this health economic evaluation. The higher dose of 50mg avapritinib is not authorised in the UK and is therefore excluded from the analysis.¹

d) Please provide an updated economic model and scenario analysis informing all modelled patient baseline characteristics based on the moderate to severe subgroup without dose escalation from PIONEER.

Baseline characteristics for the moderate to severe PIONEER subgroup excluding patients who underwent dose escalation were not available in a form that could be directly implemented in the economic model without additional post-hoc analyses.

From an economic modelling perspective, patient baseline characteristics have a limited impact on cost-effectiveness outcomes in this CEM. Of the baseline characteristics considered, starting age is the only parameter shown to have a noticeable influence on the ICER, through its effect on life expectancy and accumulated QALYs. Other baseline characteristics (e.g. sex and body weight) do not materially affect treatment costs or health state utilities.

Given the limited sensitivity of model results to baseline characteristics other than age, and the substantial additional analytical effort required to derive a full set of subgroup-specific baseline inputs, an alternative approach was adopted. The impact of restricting the population to the moderate to severe subgroup without dose escalation was assessed through a scenario analysis applying the PIONEER trial mean starting age of 51 years, which represents the primary baseline characteristic expected to differ from the base case informed by UK clinical input.

We believe this scenario provides a pragmatic and proportionate assessment of the potential impact of subgroup-specific baseline characteristics on cost-effectiveness outcomes, without introducing unnecessary analytical resource requirement.

Table 18: PIONEER baseline characteristics scenario analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
Avapritinib (PAS price)	██████████			██████████			██████████
SDT	██████████	19.18	10.33				
Scenario							
Avapritinib (list price)	██████████	15.98	9.20	██████████	0.07	0.61	██████████
Avapritinib (PAS price)	██████████	15.98	9.20	██████████	0.07	0.61	██████████
SDT	██████████	15.91	8.59				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

e) Please provide justification (e.g. based on clinical expert input) whether avapritinib dose escalation (50 mg daily dose) would be a possibility in UK clinical practice.

Avapritinib dose escalation to 50 mg once daily would not be a possibility in UK clinical practice for patients with ISM. The marketing authorisation for avapritinib in patients with ISM specifies a licensed dose of 25 mg once daily, and treatment decisions in NHS practice are expected to adhere to the licensed indication and dosing recommendations.^{1,5}

UK clinical experts consulted by the company confirmed that, in routine NHS practice, avapritinib would be prescribed in accordance with the marketing authorisation, and dose escalation beyond 25 mg would not be routinely undertaken for patients with ISM. Use of higher doses would fall outside the licensed indication and would therefore not reflect standard clinical practice in England.⁵

Consistent with this, patients who underwent dose escalation to 50 mg in the PIONEER trial were excluded from the company's base-case economic analysis to ensure alignment with licensed dosing and UK clinical practice.

f) Please provide an updated economic model and scenario analyses of the following PIONEER populations, also aligning the modelled patient characteristics:

i. The full ITT population including dose escalation

Table 19: Scenario - full ITT including escalation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	[REDACTED]	19.23	10.95	[REDACTED]	0.06	0.62	[REDACTED]
Avapritinib (PAS price)	[REDACTED]			[REDACTED]			[REDACTED]
SDT	[REDACTED]	19.18	10.33				
Scenario							
Avapritinib (list price)	[REDACTED]	19.23	10.89	[REDACTED]	0.05	0.55	[REDACTED]
Avapritinib (PAS price)	[REDACTED]	19.23	10.89	[REDACTED]	0.05	0.55	[REDACTED]
SDT	[REDACTED]	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

ii. The full ITT population excluding dose escalation

Table 20: Scenario - full ITT excluding escalation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
Avapritinib (PAS price)	██████████			██████████			██████████
SDT	██████████	19.18	10.33				
Scenario							
Avapritinib (list price)	██████████	19.22	10.78	██████████	0.05	0.59	██████████
Avapritinib (PAS price)	██████████	19.22	10.78	██████████	0.05	0.59	██████████
SDT	██████████	19.16	10.19				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

iii. The moderate and severe population including dose escalation

Table 21: Scenario – Moderate to severe including escalation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£17,743/QALY
Avapritinib (PAS price)	£1,100,000			£1,100,000			£17,743/QALY
SDT	£1,100,000	19.18	10.33				
Scenario							
Avapritinib (list price)	£1,100,000	19.22	10.76	£1,100,000	0.06	0.64	£17,188/QALY
Avapritinib (PAS price)	£1,100,000	19.22	10.76	£1,100,000	0.06	0.64	£17,188/QALY
SDT	£1,100,000	19.16	10.12				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

Model structure

B 2. Priority: The company's economic model structure included three ISM symptom severity health states based on baseline TSS thresholds consistent with PIONEER, SSM, AdvSM and death health states.

- a) Please comment on the appropriateness of using a symptom-based model structure to define mild, moderate and severe ISM, provide an overview of alternatives (e.g. based on mast cell infiltration), and comment on their plausibility.**

The use of a symptom-based model structure to define mild, moderate, and severe ISM is appropriate and consistent with both the clinical management of ISM and the available evidence base. ISM is a chronic, non-malignant condition in which disease burden is primarily driven by symptom severity rather than by short-term survival or radiographic progression. In UK clinical practice, treatment decisions and healthcare resource use are largely determined by the severity of symptoms and their impact on patients' quality of life, rather than by measures of mast cell burden alone.

The symptom-based health states applied in the model are directly informed by TSS thresholds used in the pivotal PIONEER trial, which provides the most robust comparative evidence for avapritinib in this population. This structure allows treatment effects to be modelled in terms of clinically meaningful improvements in symptoms, health-related quality of life, and associated reductions in healthcare resource use, consistent with observed trial outcomes.

The appropriateness of this symptom-based model structure was validated through consultation with three UK clinical experts experienced in the management of ISM, who confirmed that symptom burden is the primary driver of treatment decisions and healthcare utilisation in routine NHS practice.⁵

Alternative model structures based on biological markers, such as mast cell infiltration, serum tryptase levels, or KIT D816V allele burden, were considered but are less suitable for economic modelling in ISM. While these measures are relevant to disease pathophysiology, they are not routinely used in UK clinical practice to guide treatment decisions, nor are they strongly or consistently correlated with symptom burden or short-term changes in healthcare resource use. In addition, there are limited data linking changes in these biological markers to health state utilities or costs, which would introduce substantial uncertainty if used as the basis for model health states.

For these reasons, a symptom-based model structure is considered the most clinically relevant and methodologically robust approach for capturing disease burden and treatment benefit in ISM. Alternative biologically driven structures are currently implausible for economic evaluation due to limited data availability, weak linkage to patient-relevant outcomes, and limited relevance to decision-making in UK clinical practice.

b) Please elaborate on the appropriateness of using TSS to distinguish between mild, moderate and severe ISM, provide an overview of alternative outcomes, and comment on their plausibility.

The use of ISM-SAF Total Symptom Score (TSS) to distinguish between mild, moderate, and severe ISM is appropriate and clinically relevant, as symptom burden

is the primary manifestation of disease severity in patients with ISM.¹⁰ TSS captures the frequency and severity of key mastocytosis-related symptoms that directly affect patients' quality of life and healthcare utilisation, making it a suitable basis for defining clinically meaningful health states in the economic model.

TSS has been validated by clinicians as an appropriate measure of symptom burden and disease severity in ISM and is widely recognised as capturing the key disease factors assessed in routine clinical practice. In addition, consultation with two UK clinical experts confirmed that the symptom domains captured by TSS align with clinical assessment in NHS practice.⁵ One limitation noted was that dizziness is not explicitly captured within the ISM-SAF. However, dizziness would not be used in isolation to determine disease severity in clinical practice. The presence of severe dizziness alone would not result in a classification of severe disease; rather, severity assessment would require the presence and persistence of multiple relevant symptoms. As such, the omission of dizziness from the ISM-SAF is not expected to materially affect the assessment of overall disease severity or the appropriateness of TSS-based categorisation.

NHS clinical experts indicated that ISM-SAF TSS has already being used in specialist settings as part of the PIONEER trial in UK sites and is expected to play a pivotal role in the classification of disease severity going forward, particularly with the introduction of targeted therapies. In fact, the company has confirmed that ISM-SAF will be made available for NHS clinical practice speaking to its validity and importance for clinical management of ISM.

Alternative outcomes for defining ISM disease severity were considered, including biological or disease burden-based measures such as serum tryptase levels, mast cell infiltration in bone marrow, KIT D816V variant allele frequency, and composite response criteria incorporating laboratory and pathological endpoints. No other PRO measure is a viable alternative as none are specific for ISM or used in clinical practice. ISM-SAF has been specifically developed for patients with ISM and is psychometrically validated in terms of reliability and convergence with other PROMs (including PGIC, SF-12, and MC-QoL).^{8,9} Clinical experts and guidance are aligned the moderate to severe threshold of ≥ 28 TSS as the eligible population for avapritinib

which bolsters ISM-SAF as the most applicable and suitable tool for these patients.^{5,46}

At present, these alternative outcomes are less plausible for defining economic model health states, as they are not consistently used to guide treatment decisions in routine UK clinical practice and have limited direct linkage to patient-relevant outcomes such as health-related quality of life and healthcare resource use. In contrast, TSS provides a direct, patient-centred measure of disease impact that is well aligned with both clinical management and the available clinical evidence base.

c) Please provide justification for the chosen TSS categories (i.e. 0-27, 28-41 and 42-110) and provide supporting evidence (e.g. clinical guidelines) for this.

The ISM-SAF TSS categories (0-27, 28-41, and 42-110) were rigorously psychometrically derived, trial-validated, and regulator-accepted (including EMA/FDA) severity thresholds. These severity bands represent clinically meaningful distinctions in patient symptom burden, QoL impact, and clinical risk.

Through the use of a US observational study (N=103), the thresholds were established with extensive psychometric evaluations using patient global impression of symptom severity (PGIS) as an anchor. From receiver operator curve (ROC) and contingency analyses, a range of 21 to 28 was used to identify at least moderate patients. Subsequently, the cut-off value of 28 was selected as a conservative estimate for the moderate severity. For severe symptoms, divergence occurred at a cut-off value of ≥ 42 using the same analyses, differentiating these patients from those with moderate symptoms.⁹ Additionally, PIONEER phase 2 analysis of Part 1 demonstrated the reliability of ISM-SAF derived clinically meaningful groups.⁸ Notably, this evidence for the use of the ISM-SAF thresholds was accepted by the EMA regulator.⁴⁸

The threshold of TSS ≥ 28 and ≥ 42 were used in PIONEER to define moderate to severe symptoms and determine eligibility for treatment, providing a clear and empirically supported boundary for identifying patients with higher disease burden.^{4,54} The further subdivision of the moderate-to-severe range enables

differentiation between moderate and severe symptom burden, supporting more granular capture of differences in HRQoL and healthcare resource use in the model.

Several studies including the PIONEER registrational trial for avapritinib, patient surveys (TouchStone, PRISM, and Kaiser), and NHS real-world clinical practice have consistently shown that an ISM-SAF TSS ≥ 28 reliably distinguishes patients with moderate to severe ISM symptoms.^{13,14,46,54-56} Together, evidence across observational research, clinical trials, and routine care supports TSS ≥ 28 as a robust and appropriate threshold for identifying patients with significant ISM symptom burden.

The clinical relevance of these TSS categories has been validated by 3 NHS clinical experts. These experts confirmed that the proposed TSS thresholds appropriately reflect how disease severity is assessed in NHS practice and that the domains captured by TSS align with the symptoms considered most relevant when evaluating disease burden and treatment need.⁵ Definitions of mild, moderate, and severe disease based on TSS were supported as clinically appropriate, and the ISM-SAF instrument was considered valid and generalisable to the UK setting.⁵

Overall, the selected TSS categories are considered clinically meaningful, empirically grounded in the pivotal trial evidence, and validated by UK clinical experts as an appropriate framework for stratifying disease severity in ISM.⁵

d) The model structure shown in CS Figure 17 does not reflect treatment response as assessed at 24 weeks in PIONEER. Please clarify how treatment response was implemented in the economic model.

Treatment response, as assessed at 6 months (Week 24) in PIONEER, was explicitly implemented in the economic model, although this is not visually represented in the simplified schematic shown in CS Figure 17.

Specifically, at the end of cycle 6, patients receiving avapritinib were assessed against the 30% TSS response threshold, consistent with the PIONEER response definition. The proportion of patients who did not meet this threshold were discontinued from avapritinib and moved to BSC. This response-based discontinuation was implemented in the TSS sheet, where the avapritinib trace at

cycle 6 (cells T19 to V19) applies a discontinuation factor to patients remaining in the mild, moderate, and severe ISM health states.

The proportion of patients discontinuing treatment at this time point was calculated by applying the proportion of patients achieving a $\geq 30\%$ TSS reduction relative to the total health state distribution derived from the Health State Calculations sheet. Patients who met the response criterion remained on avapritinib and continued to transition across symptom severity health states in subsequent cycles, while non-responders followed the BSC pathway.

CS Figure 17 presents a high-level representation of the model structure and does not explicitly depict the 6-month response assessment or associated discontinuation rule. However, the model parameterisation fully reflects treatment response at Week 24 through an explicit, rule-based implementation aligned with the PIONEER trial design and observed responder proportions.

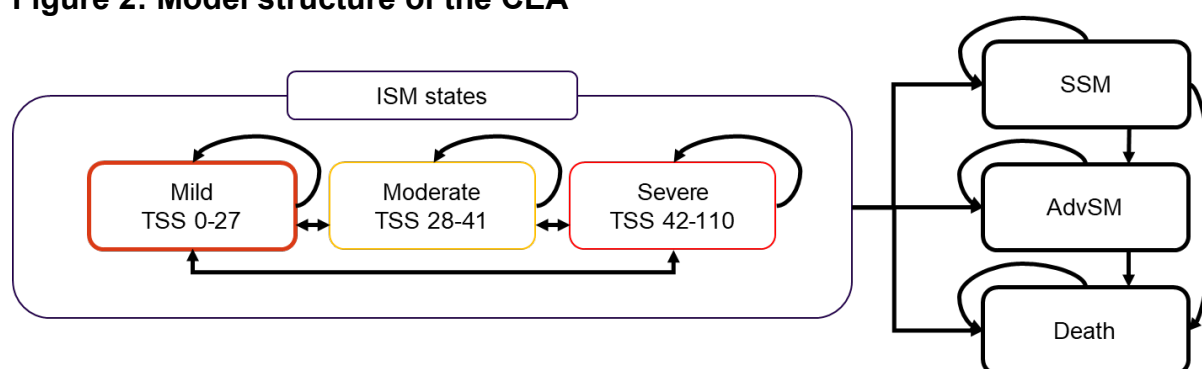
e) A small proportion of patients in the economic model transitions from ISM to SSM and AdvSM. Please clarify whether it is possible in UK clinical practice for ISM patient to progress to SSM and/or AdvSM, or whether this relates to initial misclassification.

Figure 2 replicates Figure 17 in the CS. This model structure was developed and subsequently validated by three UK clinical experts to ensure that it appropriately captures the disease progression and reflects the management pathway in the UK clinical setting.⁵

In routine practice, apparent progression from ISM to SSM or AdvSM may represent either true biological progression or reclassification of disease as additional clinical, laboratory and bone marrow information becomes available over time. The model does not distinguish between these mechanisms; instead, it applies very low transition probabilities from ISM to SSM and AdvSM to represent this small risk, in line with published natural-history data and UK expert opinion indicating that such transitions are uncommon and occur only in a minority of patients over their lifetime.^{5,51,57,58}

One UK clinical expert advised that progression from ISM to SSM is observed in a minority of patients (approximately 5–6%), with progression to AdvSM occurring in very few patients, which is similar to the magnitude of progression risk assumed based on published studies. Table 44 in the CS summarises the transition probability applied for ISM by severity to SSM and AdvSM, with ISM mild and moderate progression rates derived by proportionate scaling from the ISM severe estimates where direct evidence by severity was not available. In the follow-up engagement with UK clinical experts, the risk of progression to AdvSM was estimated at less than 5% from previous clinical experience. This is similar to the probability of progression data found in the published studies. In the absence of UK RWE, the same transition probabilities are used in the updated model.

Figure 2: Model structure of the CEA



Abbreviation: AdvSM, advanced systemic mastocytosis; ISM, indolent Systemic Mastocytosis; SSM, smouldering systemic mastocytosis; TSS, total symptom score.

- f) In the CS, it is stated that only a small proportion of ISM patients may progress to SSM and AdvSM, which was captured in the economic model by incorporating tunnel states. Considering the number of ISM patients progressing to SSM and AdvSM in UK clinical practice, please comment on whether these small numbers justify the additional modelling complexity.**

Progression from ISM to SSM or AdvSM occurs in only a small proportion of patients in UK clinical practice; however, inclusion of tunnel states to capture this progression is considered justified despite the additional modelling complexity.

Although infrequent, progression to SSM or AdvSM is associated with substantially higher morbidity, healthcare resource use, and costs, as well as distinct management pathways and prognosis compared with ISM. Excluding these progression pathways would therefore risk structurally underestimating long-term costs and health outcomes for a subset of patients, particularly over a lifetime time horizon.

The use of tunnel states allows progression to be modelled in a clinically realistic but controlled manner, ensuring that the low probability of progression observed in clinical practice is reflected while avoiding inappropriate long-term accumulation of patients in advanced disease states. Importantly, while the inclusion of these tunnel states has a small impact on overall model results, given the small numbers of patients affected, it improves the face validity and alignment with the known natural history of the disease.

Overall, while progression to SSM and AdvSM is rare, capturing these events was considered proportionate and appropriate to ensure that the model reflects clinically plausible outcomes.

g) Please provide an updated economic model and scenario analysis assuming no progression from ISM to SSM and/or AdvSM.

Table 22: Scenario - exclusion of SSM and AdvSM

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
Avapritinib (PAS price)	██████████			██████████			██████████
SDT	██████████	19.18	10.33				
Scenario							
Avapritinib (list price)	██████████	19.72	11.25	██████████	0.00	0.59	██████████
Avapritinib (PAS price)	██████████	19.72	11.25	██████████	0.00	0.59	██████████
SDT	██████████	19.72	10.66				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

- h) Please provide a cross-validation of the current model structure with other model structures of appraisals in the field of mastocytosis (including but not limited to TA1012 and TA728), and elaborate on the observed differences.**

Cross-validation of the current ISM model structure against previous NICE technology appraisals in advanced systemic mastocytosis (AdvSM) was performed versus TA728 (midostaurin) and TA1012 (avapritinib). TA728 used a partitioned survival model (PSM) with 4 states, which included progression-free survival (PFS) with sustained response, PFS with lack/loss of response, progressed disease and death. Similarly, TA1012 also used a PSM with 3 core states (progression-free, progressed disease and death), with progression-free and progressed states further split into “on” and “off” primary treatment to reflect stopping/switching; the EAG noted the TA1012 model structure was consistent with the final TA728 structure.^{53,59}

The current submission CEM fundamentally differs structurally from these AdvSM modelling approaches. Primarily, this is due to the differences between ISM and others forms of systemic mastocytosis, with the former’s principal burden consisting of long-term symptomatology and HRQoL rather than survival or progression to SSM/AdvSM. Accordingly, the model uses symptom-severity health states (with small transition probabilities to SSM/AdvSM) to capture changes in symptom burden over time, while maintaining clinical plausibility regarding the full disease spectrum. This structure was developed and validated with UK clinical experts’ input to reflect UK management pathways.⁵

Intervention and comparators

B 3. Priority: The CS comparator was SDT, implemented as a blended basket of symptomatic therapies including H1 blockers, H2-blocker (cimetidine), PPI (omeprazole), leukotriene inhibitor (montelukast), corticosteroid (prednisolone), cromolyn sodium (nalcrom), and monoclonal antibody (omalizumab). Off-label TKIs (midostaurin, imatinib, and dasatinib) were also included in the company’s base case as part of SDT. The proportion of patients on each treatment of the SDT basket was reported in CS Table 39.

- a) Please clarify why for H1-blockers an average of multiple H1-blockers was included in the SDT basket, whereas a single H2-blocker was selected to represent H2-blockers.**

For the original CS, a representative cost was used for H2-antihistamines. This has been updated in model analysis which now includes the impact of a blended basket of H2-blockers (as per agents summarised in Table 5). This has been further validated by UK clinical experts.²⁴ The average dose and cost of H2-blockers were calculated for this updated analysis. The drug costs were primarily taken from eMIT using 2024/2025 UK pounds, whereas treatments are not available on eMIT, the drug costs were referred to the BNF.^{42,60}

- b) The PIONEER trial included concomitant BSC. Please clarify what the differences are between BSC in PIONEER and the SDT comparator in the current appraisal.**

In the UK, management of ISM is primarily based on symptom-directed therapy, with treatment tailored to an individual's symptom profile rather than a single fixed regimen. NHS sources and clinical experts describe the use of medicines such as H1/H2 antihistamines, PPIs and mast cell stabilisers (sodium cromoglicate) to manage mastocytosis-related symptoms in patients with ISM.⁵ BSC in the pivotal PIONEER trial is equivalent to SDT in clinical practice as confirmed by clinicians, with the wording changed from BSC to SDT as per request from NICE.⁵ Regarding the terminology, SDT was used in CS to clearly distinguish symptomatic therapy from avapritinib, a disease-modifying TKI, which addresses the underlying pathophysiology of ISM.²⁶

- c) It was assumed that SDT therapy for avapritinib treatment responders is reduced by 50% based on the proportion of patients reduced by background therapy in the PIONEER trial. Please provide supporting evidence from PIONEER to justify this assumption and clarify whether certain SDT treatments are more likely to be reduced than others.**

The assumption that SDT use is reduced by 50% among avapritinib treatment responders is supported by evidence from the PIONEER trial demonstrating a

substantial reduction in concomitant SDT medication use following treatment initiation.

In PIONEER, approximately 54% of patients receiving avapritinib experienced an improvement in at least one SDT medication class by Cycle 37 Day 1 (Week 24).⁴ Improvements included reductions in dose or frequency, PRN use, or discontinuation of therapy. Across patients with improved SDT use, reductions were observed across multiple SDT classes, with the most frequent reductions occurring in H1-/H2-antihistamines, cromolyn sodium, and leukotriene inhibitors, which represent core components of SDT for ISM symptom management.^{4,5}

Given the heterogeneity of SDT regimens and the absence of sufficiently granular, class-specific longitudinal data suitable for economic modelling, a uniform 50% reduction in SDT use among responders was applied as a pragmatic summary of the observed reductions in BSC medication burden. This approach reflects the overall magnitude of BSC improvement observed in the trial while avoiding over-parameterisation of the model. Importantly, SDT reduction was applied only to avapritinib responders, consistent with the trial evidence that improvements in concomitant medication use were associated with symptom improvement. Patients who did not achieve a TSS response continued to receive SDT at baseline levels.

Overall, the 50% reduction assumption is considered a reasonable and conservative representation of the trial evidence, capturing clinically meaningful reductions in background therapy use without overstating cost offsets.

d) Please clarify and justify whether the proportions of patients on each treatment of the SDT basket are fixed over time, or whether they change over time (e.g. are patients allowed to switch between SDT treatments)?

The proportions of patients receiving each treatment within the SDT basket were assumed to remain fixed over time in the economic model. Patients were not permitted to switch between individual SDT components over time.

This assumption was applied consistently for both treatment arms. The relative composition of the SDT basket differs between the avapritinib and SDT arms, reflecting slight differences in SDT usage in the trial. When SDT reduction is applied

for avapritinib responders, all treatments are reduced proportionally so the relative usage of SDT remains the same.

e) Please clarify and justify whether patients can receive multiple SDT treatments simultaneously? Or monotherapy? For example, can a patient be on both an H1-blocker and a corticosteroid (prednisone)?

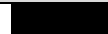
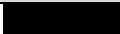
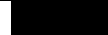
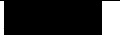
Patients were allowed to receive multiple SDT treatments simultaneously in the economic model. The SDT basket therefore reflects combination therapy, rather than mutually exclusive monotherapy options.

The SDT basket was parameterised using the average usage rates observed in the PIONEER trial, where the majority of patients received more than one class of BSC medication concurrently. This approach captures the typical pattern of SDT use in patients with moderate to severe ISM, in whom multiple therapies are commonly required to manage different symptom domains.

f) Please clarify whether the SDT basket as subsequent treatment after discontinuation of initial treatment would be different to the initial SDT basket as reported in CS Table 39, and if so, please elaborate on the differences.

Following discontinuation of avapritinib, patients were assumed to move from the avapritinib-specific SDT basket to the SDT-only basket applied in the SDT arm of the model.

Table 23: PIONEER SDT dosing proportions

Dosing of product prescribed	Proportion of product prescribed	
	SDT with Ava	SDT with placebo
H1-blocker (average)		
H2-blocker (average)		
Proton-pump inhibitor: omeprazole		
Leukotriene inhibitor: montelukast		
Corticosteroids: prednisolone		
Cromolyn sodium: nalcrom		
Monoclonal antibodies: omalizumab		

Abbreviations: H1/H2, antihistamines; SDT, symptom-directed therapy.

g) For sub-questions d) to f) regarding concomitant and subsequent treatment use, please compare the current modelling approach to what was observed in PIONEER.

Overall, the modelling approach for concomitant and subsequent SDT use is consistent with patterns observed in PIONEER, while adopting a simplified structure appropriate for economic modelling.

In PIONEER, SDT use was common and reported primarily at the class level, with patients frequently receiving multiple SDT treatments concurrently. The CEM reflects this by modelling SDT as a basket based on the average baseline SDT usage proportions observed in PIONEER, with these proportions held constant over time within each treatment arm.

Changes in SDT use observed in PIONEER were captured in the model through a simplified reduction in overall SDT use among avapritinib patients, informed by trial evidence of reduced background therapy use by Week 24. Rather than explicitly modelling class-specific switching or discontinuation, this approach applies an aggregate reduction to the SDT basket, maintaining the same relative composition across SDT components.

Following discontinuation of avapritinib, patients were assumed to move to the SDT-only basket, consistent with SDT use observed in patients managed without avapritinib. This provides a transparent and conservative representation of SDT use post-discontinuation in the absence of detailed trial data describing subsequent treatment patterns.

Overall, this approach balances consistency with PIONEER evidence and the need for clarity and simplicity in the economic model.

h) Please elaborate on the implications of the responses to the preceding sub-questions.

The modelling assumptions described in sub-questions d) to g) ensure that concomitant and subsequent SDT use is represented in a manner that is consistent with evidence from PIONEER and captures a reflective cost of SDT that would be expected in clinical practice.^{28,5,24}

By modelling SDT as a basket reflecting average baseline usage proportions and simplifying changes in SDT use over time, the model captures the overall level of background therapy use and its associated costs, without introducing unsupported assumptions regarding treatment switching or class-specific discontinuation. This approach limits structural uncertainty while preserving the key cost drivers relevant to SDT management.

Importantly, these assumptions are applied consistently across treatment arms. As a result, any simplification affects both arms in the same direction and is therefore unlikely to bias the incremental cost-effectiveness results in favour of avapritinib.

Overall, the approach provides a transparent and robust representation of SDT use that aligns with the available clinical evidence and supports stable and interpretable cost-effectiveness results.

B 4. Priority. Off-label TKIs (midostaurin, imatinib, and dasatinib) were included in the company's base case as part of SDT.

a) Please provide further justification for the inclusion of off-label TKIs, given that these were prohibited in PIONEER and currently not reimbursed in the UK.

In the follow-up engagement with UK clinical experts, reinforcing our assumption that off-label TKIs are not considered for concomitant use with avapritinib treatment but may be given if avapritinib was discontinued. Based on both previous and follow-up clinical experts' engagement, TKIs may be used as part of SDT alone, but are rarely seen in the UK clinical practice. Nevertheless, a small but non-negligible level of off-label TKIs use in ISM remains plausible.^{5,24} Given the limited evidence base supporting TKI use in ISM, there remains uncertainty regarding their real-world utilisation and clinical effectiveness. To address this, different proportions of TKI use were explored in scenario analyses to assess the impact of this uncertainty on the cost-effectiveness results in CS.

b) Please provide supporting evidence to justify the CS statement that inclusion of off-label TKIs “*was considered reflective of prescribing in clinical practice*”.

Appreciate the EAG's observation. The company proposes to clarify that TKIs are not standard UK symptomatic management for ISM, but that occasional use has been reported in highly selected circumstances.

Buonomo et al. (2022) notes that cytoreductive approaches (including TKIs) are generally not recommended unless anti-mediator therapy fails, and discusses use/role of TKIs such as imatinib in specific settings.⁶¹

Verstovsek et al. (2008) (phase II) reports dasatinib may benefit a selected group of SM patients primarily via symptom improvement, supporting that these agents have been explored/used in selected cases (albeit not routine).⁶²

Akin et al. (2022) reviews TKIs in ISM, highlighting that TKIs have been used/studied for indolent disease (historically off-label in selected patients, before/alongside newer agents).⁶³

Therefore, the company propose to reword this sentence in CS to: *“Off-label TKIs (e.g., midostaurin, imatinib, and dasatinib) were included in the base case based on observed studies indicating that TKIs have been used in a small, highly selected subgroup of non-advanced SM patients, although these agents are not routinely reimbursed or routinely used for ISM in the UK.”*

c) Please justify the modelled off-label TKI duration of 2 years. Please clarify whether patients could also discontinue off-label TKIs earlier and for what reasons, and how off-label TKI duration was modelled in other relevant NICE appraisals.

In the base case assumption, the 2-year duration was used as a conservative approach for estimating the small subset of patients receiving off-label TKIs within the SDT basket. This reflects that the use of TKIs in the UK clinical practice is infrequent; TKI treatment is typically considered only for patients with severe uncontrolled ISM treated with SDT. The evidence on typical duration in an ISM SDT context is limited.

No direct NICE appraisals were found for ISM; two NICE appraisals were found to be relevant to the SM classified disease area (specifically AdvSM):

- TA728 recommended midostaurin for treating AdvSM. It explicitly discussed uncertainty in the duration of treatment benefit for midostaurin and concluded that a 3-year treatment benefit duration would be considered for decision-making.⁵³
- TA1012 recommended avapritinib for treating AdvSM, the published committee discussion reports that a 5-year duration of treatment effect was more suitable for decision-making.⁵⁹

Therefore, a 2-year assumption is applied only to a small, off-label SDT component in the base case, with an added scenario for a 4-year duration to test the uncertainty. Also, considering patients may discontinue earlier for reasons such as insufficient clinical benefit, intolerability or adverse events, drug interaction or patient choice, a 2-year assumption of the duration of TKI use is a more conservative choice for the base case.

This approach was used to avoid overstating comparator costs in the absence of robust ISM-specific duration data, while recognising that earlier discontinuation can occur in the UK clinical practice.

d) Please justify why off-label TKIs were not included for concomitant use with avapritinib in the avapritinib + SDT arm.

Off-label TKIs were not included for concomitant use in the avapritinib + SDT arm because concurrent use of avapritinib with other TKIs is not expected in UK clinical practice.

Follow-up discussions with UK clinical experts confirmed that avapritinib would be used as a targeted therapy in place of off-label TKIs, rather than in combination with them.²⁴ In routine practice, the introduction of avapritinib for patients with moderate to severe ISM would be expected to replace the use of off-label TKIs, given overlapping mechanisms of action and the lack of evidence to support combined TKI therapy in this setting.²⁴

Consistent with this clinical input, concomitant use of off-label TKIs with avapritinib was excluded from the economic model to reflect anticipated real-world prescribing practice and to avoid modelling clinically implausible treatment combinations.

e) Please justify why off-label TKIs were not included in the avapritinib + SDT arm for patients who discontinue avapritinib treatment.

Off-label TKIs were not included in the avapritinib + SDT arm following discontinuation of avapritinib because their use is not expected to be routine in patients who discontinue avapritinib in UK clinical practice.^{5,24}

UK clinical experts advised that, for patients with moderate to severe ISM who discontinue avapritinib, subsequent management would typically revert to symptom-directed therapy, rather than escalation to off-label TKIs.^{5,24} Off-label TKIs are used infrequently in this population and are generally reserved for specific clinical circumstances; therefore, their routine inclusion as subsequent therapy following avapritinib discontinuation was not considered clinically representative.

Consistent with this clinical input and the absence of robust evidence supporting off-label TKI use in this setting, the economic model assumes that patients discontinuing avapritinib move to the SDT-only basket, avoiding inclusion of low-frequency, off-label treatments that would add uncertainty without materially affecting cost-effectiveness results.

f) Please provide an updated economic model and scenario analyses:

i. Also including off-label TKIs for concomitant use with avapritinib in the avapritinib + SDT arm.

Given clinical expert input suggests TKIs would never be used concomitantly with avapritinib, this scenario would not reflect clinical practice and therefore has not been presented.

ii. Also including off-label TKIs for patients who discontinue avapritinib treatment.

To allow for a scenario which avoids significant complexity, TKIs were applied to patients who had discontinued due to the stopping rule, and treated for two years following discontinuation from avapritinib.

Table 24: Scenario – TKI subsequent treatment for avapritinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
Avapritinib (PAS price)	██████████			██████████			██████████
SDT	██████████	19.18	10.33				
Scenario							
Avapritinib (list price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
Avapritinib (PAS price)	██████████	19.23	10.95	██████████	0.06	0.62	██████████
SDT	██████████	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

Treatment effectiveness

B 5. Priority: General treatment effectiveness and response assessment:

- a) The company did not use the ITT population as patients who had dose escalation or were in the mild state were excluded. The company also state that no imputation was performed. This may result in exclusion of patients for whom avapritinib was not effective (if that was the reason for dose escalation), and thus an over-inflation of the treatment effect. Please elaborate on the reasons for dose escalation in PIONEER and implement a scenario in which patients with dose escalation remain included, also including their additional costs.

Dose escalation to 50 mg in PIONEER Part 3 was a protocol-defined option and was not implemented as a routine escalation for patients who failed to respond at the Week 24 assessment.²⁸ Escalation was permitted only for patients who had previously demonstrated benefit and tolerability on avapritinib and subsequently experienced worsening of symptoms after entering Part 3. As such, dose escalation should not be interpreted as a marker of primary lack of efficacy at 25 mg. In the economic model, lack of effectiveness is addressed separately through the 30% TSS stopping rule at Week 24, under which patients who do not achieve a clinically meaningful response are discontinued from avapritinib. Longer-term loss of benefit was considered through time to treatment discontinuation, with clinical experts factoring in long-term response into the average time on treatment estimates.

To assess whether excluding patients with dose escalation could bias treatment effect estimates, symptom severity health state distributions were compared over time under the 30% TSS stopping rule for two populations: patients excluding those who later underwent dose escalation, and all patients including those who later escalated. Across all timepoints, the distributions of patients across mild, moderate, and severe health states were highly comparable between the two populations. At baseline, both groups show near-identical severity profiles (e.g. 0% mild / ~30% moderate / ~70% severe). Over time, improvements in symptom severity occur in both groups at a similar rate, with the proportion of patients in the mild state increasing steadily and corresponding reductions in moderate and severe states. For example, at later timepoints, the proportion of patients in the mild state ranges from approximately 75–90% when excluding escalation, compared with approximately 70–85% when including all patients, with overlapping distributions for moderate and severe disease throughout follow-up.

Table 25: Health state distributions PP versus PP excluding escalation

	PP excluding escalation (30% TSS stopping rule)			PP including escalation (30% TSS stopping rule)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Baseline	■	■	■	■	■	■
Week 4	■	■	■	■	■	■
Week 8	■	■	■	■	■	■
Week 12	■	■	■	■	■	■
Week 16	■	■	■	■	■	■
Week 20	■	■	■	■	■	■
Week 24	■	■	■	■	■	■
Week 28	■	■	■	■	■	■
Week 32	■	■	■	■	■	■
Week 36	■	■	■	■	■	■
Week 40	■	■	■	■	■	■
Week 44	■	■	■	■	■	■
Week 48	■	■	■	■	■	■
Week 56	■	■	■	■	■	■
Week 64	■	■	■	■	■	■
Week 72	■	■	■	■	■	■
Week 84	■	■	■	■	■	■
Week 96	■	■	■	■	■	■
Week 108	■	■	■	■	■	■
Week 120	■	■	■	■	■	■
Week 132	■	■	■	■	■	■
Week 144	■	■	■	■	■	■
Week 156	■	■	■	■	■	■
Week 168	■	■	■	■	■	■
Week 180	■	■	■	■	■	■
Week 192	■	■	■	■	■	■
Week 204	■	■	■	■	■	■
Week 216	■	■	■	■	■	■
Week 228	■	■	■	■	■	■

Source: Blueprint Medicines Corporation CEM [Data on file] (2025).³⁹

Importantly, exclusion of escalation patients does not result in a systematic shift towards milder disease states at any point in follow-up. In several timepoints, the proportion of patients in the severe state is comparable or slightly higher when escalation patients are excluded, indicating that exclusion does not selectively remove patients with poorer outcomes. These findings demonstrate that the

symptom severity trajectories are similar whether escalation patients are included or excluded, and that the observed treatment effect is not driven by selective exclusion of non-responders.

Overall, given that non-responders are explicitly discontinued at Week 24 under the model stopping rule, that longer-term waning is factored into time to discontinuation rather than sustained benefit, and that symptom severity distributions over time are similar when including or excluding dose escalation patients, exclusion of patients with dose escalation in the base case is unlikely to over-inflate the estimated treatment effect of avapritinib.

Table 26: Scenario – Excluding stopping rule

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
Avapritinib (PAS price)	£19.24	19.24	11.19	£0.07	0.07	0.86	£0.08
SDT	£19.18	19.18	10.33				
Scenario							
Avapritinib (list price)	£19.24	19.24	11.19	£0.07	0.07	0.86	£0.08
Avapritinib (PAS price)	£19.24	19.24	11.19	£0.07	0.07	0.86	£0.08
SDT	£19.18	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

b) Please explain whether the response assessment at 24 weeks is in line with the trial, the SmPC, or a future condition that is to be implemented in practice.

In the economic model, the 24-week response assessment was implemented as a pragmatic decision point to reflect how avapritinib is expected to be used in routine clinical practice. UK clinical experts advised that, in the absence of a licensed option for dose escalation, clinicians would be expected to formally assess treatment

benefit within the first 6 months of therapy and discontinue avapritinib in patients who do not demonstrate a clinically meaningful improvement in symptoms.⁵

This approach reflects standard clinical principles for targeted therapies in chronic conditions, where continuation of treatment is contingent on evidence of benefit, even if a specific response assessment timepoint is not mandated in the SmPC. Although the SmPC does not explicitly specify a 24-week stopping rule, regular reassessment of treatment effectiveness is anticipated, and a 6-month timeframe was considered clinically reasonable and appropriate.¹

c) Please provide justification for the response criteria, i.e. the 30% and 50% reduction in TSS thresholds.

UK clinical experts validated both thresholds as clinically relevant for decision-making.⁵ Across three UK clinical experts, 30% reduction of TSS was consistently considered sufficient to support continuation of treatment and clinically valuable for patients, while 50% reduction was described as a higher (“gold standard”) threshold indicating a more substantial response. Clinical experts also noted that clinical judgement would allow some flexibility around the threshold (e.g., near-threshold improvements may still be meaningful in practice), however, 30% represented a reasonable binary input for modelling.⁵

These response criteria are bolstered by psychometric validation in an observational cohort and PIONEER Part 1 which showed a 30% decrease in TSS was clinically meaningful.^{8,9} Furthermore, this response criteria was highlighted by the ECNM-AIM consortium as a clinically significant response.⁴⁶ A 50% reduction in TSS was identified as an even more conservative threshold improvement in psychometric validity tests, therefore, it was included as an additional secondary endpoint for response.^{4,8,9}

d) The proportion of responders was calculated as an average from all health states. Please consider a scenario where response rates are not averaged but applied to the health state they were derived from and comment on the implications of using an average.

In the CEM, the responder proportions are not calculated as a simple average across health states. Instead, they are derived from the health state–specific distributions in the model and are calculated using the health state occupancy from which they are derived (see the Health State Calculations sheet). In practice, the proportion of responders at the response assessment reflects the share of patients remaining in the responder distribution relative to the total patient distribution at that timepoint, rather than applying a flat average response rate across all health states.

Therefore, the request to apply response rates to “the health state they were derived from” is already implemented in the current model. The statement in the CS that responder proportions were calculated as an average from all health states was a representative description that showed the averages but in the actual model response rates are used for each health state.

e) The company writes in Section 3.4.2: “The model base case assumes 10 minimum of patients required for this analysis, and the model explored 0 and 30 minimum of patients in the scenario analyses.” It is unclear to the EAG what is meant by this, but it appears to be important as scenarios are performed on this. Please explain.

The reference to a “minimum of patients required for this analysis” relates to a data-stability rule applied when deriving health state distributions from the PIONEER trial data in later follow-up cycles.²⁸

In the final cycles of follow-up, the number of patients contributing TSS data decreases substantially due to trial drop-out, censoring, or patients not having a recorded assessment at that timepoint. When very small numbers of patients contribute data, the resulting health state distributions can become unstable and unrepresentative (for example, a single remaining patient in the mild state would imply 100% occupancy of that state).

To mitigate this issue, the base-case applied a minimum threshold of 10 patients contributing data at a given cycle for that cycle’s health state distribution to be used directly. This threshold was not intended to represent a clinical assumption, but

rather a pragmatic modelling rule to avoid spurious changes in health state occupancy driven by very small sample sizes.

Scenario analyses exploring thresholds of 0 patients (i.e. no minimum applied) and 30 patients were conducted to assess the sensitivity of model outcomes to this assumption. These scenarios demonstrated the impact of allowing distributions to be driven by very small numbers of patients versus imposing a more conservative stability requirement.

B 6. Priority: Avapritinib treatment effect:

a) The company used trial health state occupation directly in the model.

Please elaborate on the advantages and disadvantages of this approach, as opposed to calculating transition probabilities.

A Markov model based on estimated transition probabilities was considered but not adopted, as it was not expected to add value in the context of ISM treated with avapritinib.

Evidence from PIONEER, supported by UK clinical expert input, indicates that treatment benefit is achieved early (within 3 to 6 months) and is then largely maintained over time.⁵ After this initial response period, symptom severity is stable, with a high proportion of patients remaining in the mild health state and only limited movement between health states in later cycles (approximately 5–15% of patients transitioning per cycle). Under these conditions, a Markov structure would imply very low transition hazards beyond the early phase, offering little additional insight compared with directly using observed health state occupancy.

In addition, estimating reliable transition probabilities would be challenging due to the small number of observed transitions, particularly at later timepoints as patient numbers decline. Transition estimates would therefore be sensitive to modelling assumptions and functional form choices, increasing structural uncertainty without clear benefit. Given these limitations, the use of observed trial health state occupancy was considered a more transparent and proportionate approach.

b) Please implement an alternative modelling approach where transition probabilities are estimated from the trial, either using multi-state survival analysis or simpler spline-based approaches, e.g. estimating annual transition probabilities (and converting them to the model cycle length), while considering the possibility of competing events, e.g. by following the Gidwani et al tutorial (<https://pubmed.ncbi.nlm.nih.gov/32797380/>).

The company considered the requested alternative approach of estimating transition probabilities from the trial using multi-state survival or spline-based methods with competing events. However, this approach was not implemented because the current model already incorporates safeguards to avoid overfitting, and a transition-probability framework would require additional assumptions that are not supported by the available data.

In the current model, potential overfitting to late-cycle trial data is mitigated by applying a minimum patient threshold of 10 when deriving health state distributions. In later cycles, patient numbers decline due to censoring and missing assessments; without this rule, health state occupancy could be disproportionately influenced by a very small number of patients (e.g. one patient driving 100% occupancy of a state). The 10-patient threshold ensures that observed health state distributions reflect a stable, representative sample, rather than idiosyncratic outcomes. Scenario analyses exploring alternative thresholds (0 and 30 patients) further demonstrate that results are not driven by this assumption, supporting its effectiveness as an anti-overfitting safeguard.

By contrast, implementing a transition-probability approach would require several explicit assumptions that go beyond the available evidence. These include: (i) specification of which transitions are permitted between symptom severity states at each time point, (ii) selection of functional forms for time-varying transition hazards or spline structures, (iii) assumptions regarding the persistence of early-treatment effects versus long-term convergence, (iv) handling of sparse transition counts in later cycles, and (v) specification of competing events (e.g. discontinuation) and their interaction with symptom-state transitions. Given the limited number of observed transitions—particularly beyond the early response period—estimated transition

probabilities would be highly sensitive to these assumptions and could amplify noise rather than reduce it.

Overall, the current approach, combining observed health state occupancy with a minimum patient threshold and sensitivity analyses, provides a transparent and robust means of reflecting trial outcomes while limiting overfitting. Implementing a transition-probability framework would introduce additional structural assumptions and uncertainty, with limited expectation of improving the accuracy or interpretability of model results. Ultimately, it would be expected that a transition probability engine would not materially change the ICER result of the CEM, as the transitions would assume a relatively stable health state occupancy in the extrapolation past the trial period, which would mimic the current approach of maintaining the current health state.

c) After the end of the open label extension (OLE), it is assumed that patients remain in the last health state for the duration of the modelled time. Please justify why this is a reasonable assumption as opposed to allowing for transitions when the OLE study has finished, in particular reflecting on whether and to what extent transitions were observed in the last two years of follow-up.

After the end of the open-label extension (OLE), patients were assumed to remain in their last observed symptom severity health state for the remainder of the modelled time horizon. This assumption is supported by evidence from the later years of follow-up, which indicate stabilisation of symptom burden and limited clinically meaningful transition activity.²⁸

In the final two years of available OLE data, transitions between symptom severity health states were infrequent. The majority of patients remained in the same health state across consecutive assessment cycles, most commonly in the mild state, indicating maintenance of treatment effect rather than ongoing improvement or deterioration.⁶⁴ Where transitions were observed, they affected only a small proportion of patients per cycle.

Importantly, analysis of patients who did change health state during this later period shows that the average within-patient change in TSS was small, with changes clustered around health state thresholds rather than reflecting substantial shifts in symptom burden.⁶⁴ This pattern suggests that late transitions are largely driven by modest variability in patient-reported symptoms rather than sustained progression or regression. As such, these movements do not indicate a continued dynamic disease process that would justify extrapolating ongoing transition probabilities beyond the observed follow-up.

Allowing further health state transitions after the end of the OLE would therefore require extrapolation of behaviour that is not supported by the available data and would necessitate additional assumptions regarding the direction, magnitude, and durability of symptom changes. Given the small average TSS changes observed among patients who transitioned late in follow-up, any such extrapolated transitions would be highly uncertain and unlikely to materially influence model outcomes.

Assuming patients remain in their last observed health state after completion of the OLE provides a conservative and transparent approach to extrapolation. It reflects the observed stabilisation of symptoms in long-term follow-up and avoids introducing unsupported late transitions that could artificially inflate either ongoing benefit or delayed deterioration. This assumption is also consistent with UK clinical expert input, which supports the view that avapritinib's primary symptom benefit is achieved earlier in treatment and is then largely maintained over time.

Overall, maintaining patients in their final observed health state after the end of the OLE represents a reasonable, evidence-aligned modelling choice that balances fidelity to the observed data with avoidance of unnecessary extrapolation uncertainty.

d) Please explain whether the OLE data in the avapritinib arm included those that had crossed over after the first 24 weeks. If crossed over patients are included in the modelling of the avapritinib arm of the model (post 24-weeks), was a response assessment at 24 weeks after they started treatment included in the modelling for these patients? Please justify your approach and provide a scenario in which patients who

crossed over are excluded (if this is not the base-case) and one where they are included with a response assessment 24 weeks after they started treatment.

The OLE data used to inform the avapritinib arm did not include patients who crossed over from SDT to avapritinib after the initial 24-week period. Following crossover, these patients were treated as avapritinib recipients and contributed to the avapritinib health state distributions from that point onwards. This approach allows all available post-crossover avapritinib exposure data to be used to inform longer-term symptom severity outcomes, increasing the robustness of the health state estimates and avoiding unnecessary exclusion of relevant trial evidence.

Table 27: Scenario – Health state occupancy excluding crossover patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.06
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.06
SDT	£19.18	19.18	10.33				
Scenario							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.06
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.06
SDT	£19.18	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-years; SDT: Symptom-directed therapy; PAS: Patient Access Scheme.

e) Please also confirm that patients in the mild state who crossed over were not included in the modelling, and exclude them if they were included.

Yes, we can confirm that crossover patients that started treatment as mild were excluded from the distribution.

B 7. Priority: Treatment effect of SDT:

- a) While Table 43 of the CS report states that no patients in the SDT arm reside in the mild state at baseline, in the model, a percentage of patients in the SDT arm does start in the mild state at baseline. This means that there is no like for like comparison. Please correct the model if needed, and justify your modelling choice.**

Appreciated. This arose from an unintended duplication in the CHOOSE formula used to select the model population in the “Efficacy” page.

There are 4 drop-down options under the defined name “population_selection”, from option 1 to 4, which are: All; Moderate to severe; All (no dose escalation); Moderate to severe (no dose escalation). However, the CHOOSE function was given 5 reference cells, meaning the selected data could map to the incorrect patient group. Here is the breakdown of reference cells prior to correction:

'Health state by population'!F86 – referring to option 1

'Health state by population'!U86 – referring to option 2

'Health state by population'!AJ86 – referring to option 3

'Health state by population'!AJ86 – duplication of option 3. (Error deleted)

'Health state by population'!AY86 – referring to option 4

Because option 4 in the formula duplicated option 3, selecting “Population_choice”=4 returned the same cell as option 3. After deleting the duplication, the formula used in the current model is presented as:

“=CHOOSE(Population_choice,'Health state by population'!F86,'Health state by population'!U86,'Health state by population'!AJ86,'Health state by population'!AY86)”

- b) In the CS report section 3.4.2.2 it is stated: “In the model, SDT patients were therefore assumed to return to their baseline health state distribution beyond 24 weeks.” This was justified by patients not being expected to transition between disease severity states in the absence of a change in treatment. To the EAG this appears to be a justification for**

remaining in the same health state that patients were in at 24 weeks, particularly as it is unclear why patients would discontinue effective treatment in clinical practice, which is the assumption the company appears to be making. In addition, no detail is provided on how the “waning period” is implemented. Please explain and justify your modelling approach, and provide a scenario in which patients remain at their 24-week health state.

The statement in CS Section 3.4.2.2 does not imply that patients discontinue effective SDT at 24 weeks. Rather, it reflects clinical expert input that, in the absence of a change in treatment, patients receiving SDT would not be expected to experience a sustained change in underlying symptom severity compared with baseline.

UK clinical experts advised that SDT provides symptomatic control but does not modify the disease course in ISM.⁵ As such, patients remaining on SDT would be expected to have a stable symptom burden over time, broadly consistent with their baseline severity. Any changes observed during the trial period are not expected to represent true disease progression or improvement, but may instead reflect trial-related factors, including a treatment effect associated with increased clinical attention or reporting variability in patient-reported outcomes such as the ISM-SAF, which is subject to patient perception and reporting behaviour (i.e. subject to a placebo effect).

Accordingly, beyond 24 weeks, the model assumes that patients in the SDT arm return to their baseline health state distribution, representing the expected long-term symptom severity for patients continuing on SDT without a change in therapy. This approach does not represent a “waning” of treatment effectiveness or treatment discontinuation but rather reflects the expectation that SDT maintains symptoms at baseline levels over time.

The term “waning period” refers to the point at which any short-term trial-related changes in reported symptom severity are no longer assumed to persist, rather than to a loss of treatment benefit. In the model, this is implemented by holding the SDT health state distribution constant at baseline beyond 24 weeks.

To address the EAG request, a scenario can be provided in which SDT patients are assumed to remain in their 24-week health state distribution indefinitely, rather than reverting to baseline. This scenario explores the impact of assuming that observed 24-week symptom severity under SDT is maintained long-term and allows the sensitivity of results to this assumption to be assessed.

Overall, the base-case approach reflects clinical expectations regarding the long-term symptom profile of patients remaining on SDT, while the proposed scenario provides a transparent alternative aligned with the trial observations.

B 8. Progression to Smouldering SM (SSM) and advanced SM (AdvSM):

- a) Please explain whether transitions to SSM and advSM were estimated in the severe ISM population in the literature provided and discuss the generalisability of this source for the present decision problem.

The progression evidence used (Trizuljak et al., 2020; Escribano et al., 2009; Matito et al., 2013) reports transitions by diagnostic category (e.g., ISM → SSM/AdvSM and SSM → AdvSM) and does not estimate progression risks stratified by symptom-defined severity within ISM (i.e., mild, moderate, and severe as defined by TSS). As such, the literature does not provide progression estimates directly applicable to the model's symptom-based ISM health states.

To translate this evidence into the symptom-based model structure, the published ISM-level progression estimates were anchored to the severe ISM health state. Severe ISM was selected as the anchor because it represents the subgroup most likely to reflect the higher-risk end of the ISM spectrum captured in observational cohorts reporting progression. This anchoring is clinically plausible given that greater disease severity is generally associated with increased biological activity and higher likelihood of progression, even though severity in the literature is defined at the disease-category level rather than by symptom burden.

These sources are considered generalisable to the present decision problem because they describe the natural history of systemic mastocytosis under routine clinical management and consistently show that progression from ISM to SSM or AdvSM is rare but possible over long-term follow-up. Progression to advanced

disease is driven primarily by underlying disease biology rather than short-term symptom management, meaning that category-level progression risks from international observational cohorts are applicable for informing progression pathways in UK practice.⁵ In addition, Matito et al. demonstrate that progression risk increases with greater disease-category severity (e.g., higher progression risk from SSM to AdvSM than from ISM), supporting the principle that anchoring progression risk to the severe ISM state provides a conservative and clinically credible basis for modelling progression within ISM.⁵⁸

- b) Please provide justification and supporting evidence for the assumption that patients can transition to SSM and advSM from the mild and moderate SM states and the assumptions on the magnitude of these estimates.

The model applies stratified progression risks (mild, moderate, severe) to reflect a clinically plausible relationship between symptom severity and the likelihood of progression to SSM and AdvSM. While the literature informing progression (Trizuljak et al., 2020; Escribano et al., 2009; Matito et al., 2013) reports progression primarily at the disease-category level (ISM/SSM/AdvSM) rather than by symptom-defined strata, it supports the underlying principle that progression risk increases with greater disease severity.

In particular, Matito et al. show a clear severity gradient across diagnostic categories, with progression risk higher in more severe categories (e.g.,⁵⁸ This provides supportive evidence for applying a severity-ordered structure within the model, i.e. higher progression from SSM to AdvSM than from ISM).⁵⁸ This provides supportive evidence for applying a severity-ordered structure within the model, i.e. assigning higher progression risk to patients with greater disease burden. Trizuljak et al. and Escribano et al. similarly describe progression from ISM as an uncommon event over long-term follow-up, supporting the use of small transition probabilities overall, while allowing these risks to be higher in the subgroup most likely to reflect higher underlying risk.^{51,57}

Given the absence of published estimates stratified by symptom severity within ISM, the model operationalises this principle by anchoring progression risk to the severe ISM health state and applying lower risks to moderate and mild ISM using

transparent scaling assumptions. This approach maintains consistency with the low overall progression rates reported in the literature while incorporating a clinically plausible gradient of increasing progression risk with increasing symptom severity.

B 9. Priority: Treatment discontinuation

a) It is unclear what reasons are for treatment discontinuation of avapritinib. Presumably, reasons include adverse events, loss of response and potentially stopping rules. Please elaborate on reasons for treatment discontinuation and to what extent these were observed in PIONEER.

In PIONEER, treatment discontinuation occurred for a range of reasons, which are summarised in Table 22. A total of █ participants discontinued treatment across Parts 1, 2 and 3, with the most frequent reason being withdrawal by subject (█ patients), often due to a lack of perceived clinical benefit or the decision to switch to commercial avapritinib. AEs led to █ discontinuations, including cases of neutropenia, diarrhoea, dizziness and acute myocardial infarction. Physician decisions (█ participants) were primarily based on uncontrolled symptoms or transitioning patients to commercial supply, while progressive disease (█ participants) involved the evolution of SM into advanced forms or secondary mast cell leukaemia. The remaining █ discontinuations were attributed to non-compliance (█ participants), being lost to follow-up (█ participants), death (█ participant), pregnancy (█ participant) or other factors such as planning a family, starting a new clinical trial or a general lack of effectiveness (█ participants).³⁵

Table 28. Summary of reasons for study discontinuation and associated context among participants who discontinued PIONEER study (N=█)

Reason for discontinuation	Further context
Withdrawal by subject (N=█)	• Withdrawal of consent due to lack of perceived benefit • Worsening or persistent symptoms • Burden of study participation or frequency of study visits • Feeling overwhelmed or stressed by the study • Decision to pursue standard of care outside the study • Enrolment in or intention to enrol in another clinical trial • Personal or family circumstances • Refusal of study procedures (e.g. blood collection)

Reason for discontinuation	Further context
	Unspecified personal decision
AE (N=■)	- TEAEs leading to discontinuation - Haematological events (e.g. decreased neutrophil count) - Neurological events (e.g. pseudo-seizures, involuntary movements, dizziness) - Gastrointestinal events (e.g. diarrhoea) - Cardiovascular events (e.g. myocardial infarction) - General or systemic events (e.g. pain in lower limbs, weight loss, shortness of breath, delirium) - Serious events including progression to acute myeloid leukaemia
Physician decision (N=■)	- Lack of meaningful clinical, biochemical or pathological response - Safety concerns requiring discontinuation - Protocol-mandated discontinuation - Decision to switch to commercial avapritinib supply
Progressive disease (N=■)	- Clinical progression of systemic mastocytosis - Progression to advanced systemic mastocytosis - Evolution to secondary mast cell leukaemia or mast cell leukaemia
Non-compliance (N=■)	- Failure to adhere to study drug administration - Failure to comply with protocol-required study visits or procedures
Lost to follow-up (N=■)	- Participant could not be contacted for ongoing follow-up - Participant did not return for scheduled study visits
Death (N=■)	Death occurring during the study or follow-up period
Pregnancy (N=■)	- Pregnancy during the study - Decision to discontinue in order to pursue pregnancy
Other (N=■)	- Lack of effectiveness not otherwise specified - Decision to start a new clinical trial - Desire for dose escalation not permitted under the protocol - Participant decision not further specified

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event
Source: Blueprint Medicines Corporation Additional Efficacy Data (2025)²⁸

For further details on the number of patients who discontinued avapritinib, the reasons (including adverse events or disease progression) and the timing, see Table 15 and Table 16.³⁵

b) Please explain what transition probabilities are applied to patients in the avapritinib arm that discontinue before week 24. Please provide a table

overview showing how the modelled health state distributions up to week 24 compare with trial data with respect to patients on avapritinib and SDT in the avapritinib arm.

In the avapritinib arm, discontinuation prior to Week 24 is modelled as discontinuation due to AEs, informed by PIONEER (Table 49 in CS). This is applied at cycle 3 (Week 12), based on the proportion of patients discontinuing avapritinib due to AEs observed in PIONEER by that timepoint.

Patients who discontinue avapritinib prior to Week 24 are assumed to receive no ongoing treatment benefit from avapritinib. From the cycle of discontinuation onwards, these patients are re-distributed according to the SDT health state distribution and follow the SDT symptom-severity trajectory for the remainder of the pre-Week 24 period (and beyond), consistent with management without avapritinib.

Table 30 presents the avapritinib-arm health-state distributions from the economic model (normalised to 100% across ISM health states, i.e. excluding mortality) alongside the corresponding trial-based distributions. Results are shown for the population excluding patients with mild disease at baseline and those receiving dose escalation. Trial distributions are reported at Week 24 and reflect application of the $\geq 30\%$ TSS improvement stopping rule. The model predicts slightly poorer health-state occupancy compared with the trial estimates, driven by the inclusion of SDT health-state occupancy for patients who discontinue avapritinib over time.

Table 29. Health state distribution of avapritinib arm for ISM states

Model estimates for health state distribution (moderate to severe excluding dose escalation)									
Time	Avapritinib + SDT			Avapritinib discontinued			Total		
	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Baseline	■	■	■	■	■	■	■	■	■
Week 4	■	■	■	■	■	■	■	■	■
Week 8	■	■	■	■	■	■	■	■	■
Week 12	■	■	■	■	■	■	■	■	■
Week 16	■	■	■	■	■	■	■	■	■
Week 20	■	■	■	■	■	■	■	■	■
Week 24	■	■	■	■	■	■	■	■	■
Trial estimates for health state distribution (moderate to severe excluding dose escalation)									
Baseline	NA						■	■	■
Week 4	NA						■	■	■
Week 8	NA						■	■	■
Week 12	NA						■	■	■
Week 16	NA						■	■	■
Week 20	NA						■	■	■
Week 24	NA						■	■	■

Abbreviations: ISM, indolent systemic mastocytosis; NA, not applicable.

Source: Blueprint Medicines Corporation CEM [Data on file] (2025).³⁹

- c) The company includes a treatment stopping rule at 24 weeks in case of non-response. In addition to this, it appears that the company models continuous constant treatment discontinuation, which was basically based on expert opinion, which in turn was informed by survival analysis in a US real world evidence (RWE) study, as well as discontinuation caused by adverse events (AE) in the first model cycle. The US data and expert opinion may have included those that discontinued due to non-response and adverse events, particularly if no formal response assessment was in place. In this case the company's approach would be double-counting treatment discontinuation. Please reflect on this and provide additional justification for the chosen approach.

The company's approach does not double count discontinuation because the 24-week stopping rule and long-term discontinuation represent distinct mechanisms applied to different patient groups and time periods.

The 24-week stopping rule applies specifically to initial non-responders. Patients who do not achieve the response criterion at Week 24 are discontinued at that point and do not contribute to long-term time on treatment. Separately, discontinuation due to AEs in the early model period is applied to reflect short-term tolerability-related stopping observed in PIONEER.

In contrast, the long-term discontinuation function is intended to reflect the average expected duration of treatment among patients who demonstrate an initial response and continue beyond the 24-week assessment. This discontinuation is not intended to capture early non-response or early AE-driven stopping; rather, it represents the expected time on avapritinib in clinical practice for responders, informed by clinical expert judgement and external persistence evidence.

UK clinical experts considered that responders would not remain on avapritinib indefinitely and identified several clinically plausible reasons for longer-term discontinuation, including: (i) loss of long-term benefit (waning of treatment effect), (ii) AEs arising over longer exposure, (iii) changes in the treatment landscape over the next decade (e.g. updated guidance or new treatment options), and (iv) patient-level factors such as changes in personal circumstances and preferences.⁵

Therefore, the long-term discontinuation is representative of expected treatment persistence in responders and captures real-world clinical dynamics not addressed by the Week 24 non-response rule.

While it is possible that US RWE persistence data include discontinuations for a range of reasons (including non-response and AEs), the model's implementation ensures that early discontinuation mechanisms are handled explicitly via the Week 24 stopping rule and early AE discontinuation, with the long-term discontinuation applied to the responder population continuing beyond this initial period. As such, the approach reflects overall expected time on treatment for responders and avoids structurally double counting early stopping events.

- d) The US RWE data is said to include patients with SM. Please confirm that the patients used to analyse DoT had moderate to severe indolent SM and if this is not the case, please provide a breakdown of health states of patients included in the dataset, also on whether patients with SSM and advSM were included.**

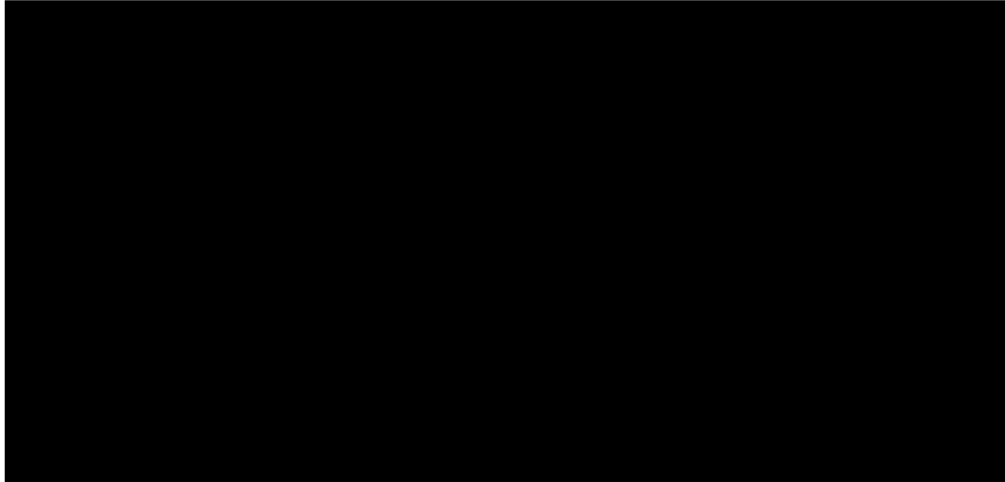
The US RWE dataset used to inform DoT included patients recorded as having systemic mastocytosis (SM); however, health states (mild, moderate, severe) were not recorded and SM subtype information was incomplete. As a result, it is not possible to confirm that all patients included in the primary DoT analysis had moderate to severe ISM, nor to provide a breakdown of patients by symptom severity health state. Notably, this is due in part to the fact that US patients are treated with avapritinib 25mg under a broader label of 'adults with ISM'.⁴⁷

To address this limitation, the primary analysis used starting dose (25 mg) as a pragmatic proxy for the ISM population, as 25 mg is the starting dose used in ISM. This approach maximised the available sample size for estimating DoT (Analysis 1; n=864). While this may include patients without recorded subtype, it provides the most statistically stable estimate of treatment persistence.²⁹

Where subtype information was available, additional analyses were conducted restricting the dataset to patients recorded as ISM (Analysis 2; n=632) and further to ISM without dose escalation (Analysis 3; n=542). Although these restrictions reduce the size of the dataset, the estimated DoT curves across Analyses 1–3 show very similar trends, as illustrated in the accompanying figures. This consistency provides reassurance that the estimated DoT is not materially sensitive to the specific population definition used, albeit with substantial uncertainty that is reflected in the model.²⁹

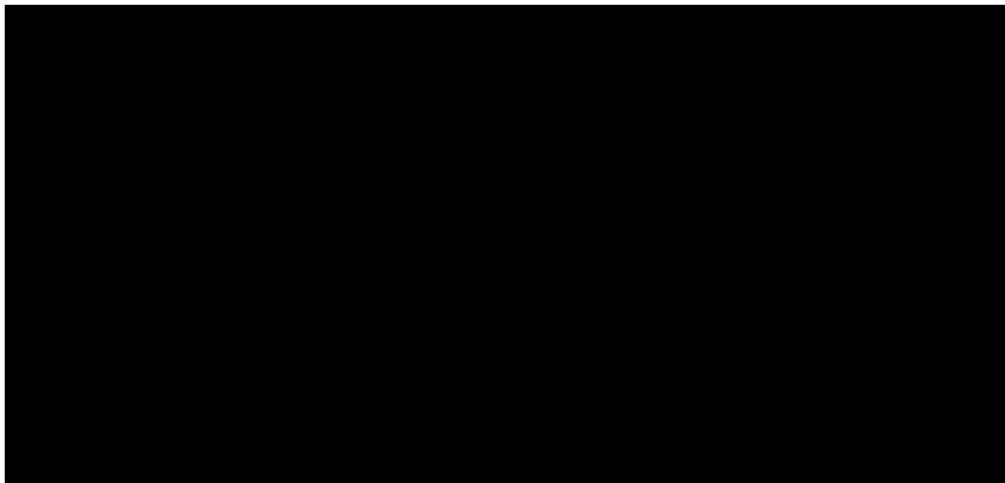
Overall, although the US RWE data do not allow confirmation of moderate to severe ISM or a health state breakdown, the use of a pragmatic proxy combined with sensitivity analyses supports the robustness of the DoT assumptions.

Figure 3: US RWE Kaplan Meier analysis 1 (combined curves – 240 months)



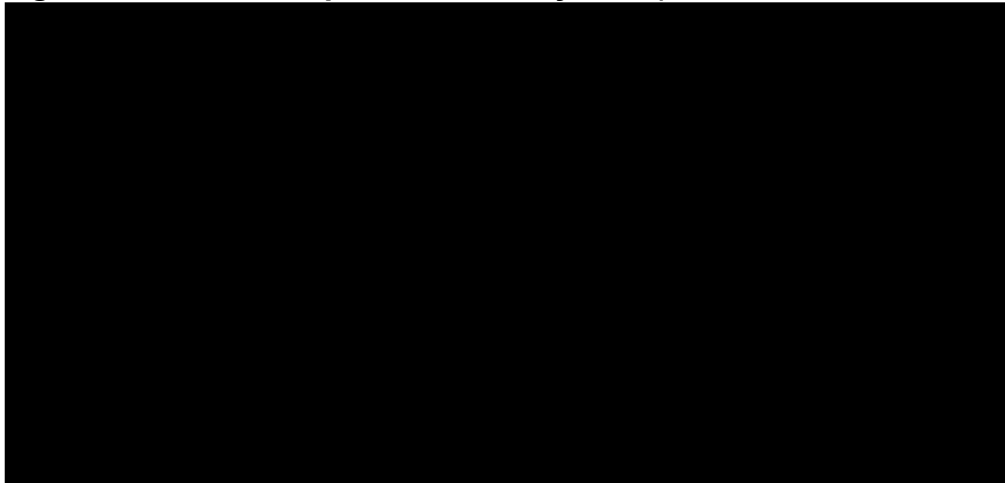
Abbreviations: KM, Kaplan Meier; RWE, real-world evidence.

Figure 4: US RWE Kaplan Meier analysis 2 (combined curves – 240 months)



Abbreviations: KM, Kaplan Meier; RWE, real-world evidence.

Figure 5: US RWE Kaplan Meier analysis 3 (combined curves – 240 months



Abbreviations: KM, Kaplan Meier; RWE, real-world evidence.

e) The company state that the PIONEER data were not mature enough to generate reliable extrapolations to inform duration of treatment (DoT). However, the resulting distributions from the survival analysis on the US RWE data also resulted in vast long-term differences and therefore uncertainty, which is now not included in the base-case (where an average DoT is assumed and applied via a constant transition probability). Please provide a table overview of proportions on treatment at different timepoints (and at least up to 12 years) in the PIONEER study (moderate to severe ISM with and without dose escalation) and in the health economic model company base-case as well as in a scenario in which the treatment response discontinuation rule is disabled.

Yes, the US RWE analyses demonstrated substantial uncertainty in long-term DoT extrapolations, with wide variation across fitted survival functions and materially different long-term persistence estimates.²⁹ Given this uncertainty, and the immaturity of PIONEER for informing long-term DoT, UK and Dutch clinical expert opinion was relied upon to inform the expected average duration of treatment among patients who initially respond to avapritinib. clinical experts advised that long-term continuous treatment beyond a finite period is unlikely in routine practice, with discontinuation over time expected for a range of clinical and practical reasons.^{5,44}

Table 29 provides the observed Kaplan–Meier proportions on treatment in PIONEER. As shown, PIONEER provides observed persistence up to 60 months; proportions beyond this timepoint (e.g., up to 12 years) are not available from PIONEER at present and therefore are not presented.³⁵

Table 30: Proportion of patients on treatment in PIONEER

Timepoint	PIONEER Placebo →25 mg (N=■)	PIONEER Avapritinib 25→25 mg/NA (N=■)	PIONEER pooled Placebo/ Avapritinib 25→25 mg/NA (N=■)
3 months	■	■	■
6 months	■	■	■
9 months	■	■	■
12 months	■	■	■
18 months	■	■	■
24 months	■	■	■
30 months	■	■	■
36 months	■	■	■
42 months	■	■	■
48 months	■	■	■
54 months	■	■	■
60 months	■	■	■

Source: Blueprint Medicines PIONEER Additional Efficacy (data on file).³⁵

- f) Based on the findings from the previous sub-question, please revise the approach chosen for modelling treatment discontinuation accordingly. This could entail removing the responder-based discontinuation rule, or using survival analysis on the RWE or PIONEER data to estimate long-term treatment discontinuation (following TSD 14).**

Based on the evidence and limitations described in (c)–(e), the company considers the current approach to modelling treatment discontinuation to remain appropriate and does not propose removing the responder-based stopping rule or replacing the base-case with a fully survival-analysis–driven DoT extrapolation.

The 24-week responder assessment is retained because it reflects clinical expectations that patients who do not achieve clinically meaningful symptom improvement would not continue avapritinib in routine practice, and it avoids carrying forward long-term costs and benefits for patients who do not respond. In addition, the PIONEER follow-up remains insufficient to support reliable long-term persistence extrapolation, and the US RWE survival analyses produced materially different long-term tails with substantial uncertainty.²⁹ As such, adopting any single fitted DoT curve from PIONEER or RWE as the base case would introduce additional structural

uncertainty and make results highly sensitive to parametric choice and sparse long-term data.

Therefore, the base case continues to use clinical expert-informed average DoT for responders applied via a constant discontinuation probability, with early discontinuation and stopping handled explicitly (AEs early; non-response at Week 24).⁵ This approach provides a transparent, clinically plausible representation of expected time on treatment while avoiding undue reliance on unstable long-term extrapolations.

g) Please also explain whether patients discontinued in all health states equally and elaborate on the plausibility of this assumption, including evidence from PIONEER in the justification. Please explore alternative assumptions (e.g. increasing risk of treatment discontinuation in more severe health states) in scenario analysis.

In the base-case model, long-term treatment discontinuation is applied uniformly across all symptom severity health states, with all responding patients assumed to discontinue at the same average DoT. This reflects a simplifying assumption intended to represent the expected average duration of treatment among responders, informed by UK clinical expert input, rather than modelling differential persistence by health state.⁵

This assumption is considered conservative. In clinical practice, it would be reasonable to expect patients with more severe symptoms to have a higher likelihood of discontinuation over time (e.g. due to tolerability concerns or perceived benefit–risk balance), while patients achieving sustained symptom control would be more likely to remain on treatment.⁵ By assuming equal discontinuation across all health states at the same timepoint, the model does not preferentially retain patients with better outcomes and therefore avoids overstating long-term treatment benefit.

At present, the PIONEER data are not sufficiently mature to robustly assess health state–specific long-term discontinuation patterns. As such, applying differential long-term discontinuation rates by health state would require assumptions not directly supported by the trial evidence.

Given that all patients are assumed to discontinue at the selected average DoT in the base case, scenarios in which more severe patients discontinue earlier cannot be implemented without introducing additional speculative structure. Nevertheless, the company recognises that an alternative assumption—such as increasing risk of long-term discontinuation in more severe health states—is clinically plausible and would be expected to result in greater retained benefit among patients remaining on treatment. The uniform-discontinuation assumption therefore represents a cautious and transparent choice in the face of uncertainty.

Overall, applying equal long-term discontinuation across health states provides a conservative representation of treatment persistence, consistent with limited trial maturity and high uncertainty in external persistence data, while ensuring that model outcomes are not biased in favour of avapritinib.

h) For patients in the SDT arm, no treatment discontinuation was assumed. For some of the treatments in the blended comparator, it may be possible to identify average treatment durations. For example, it does not appear likely that patients will continue on TKIs indefinitely. This would imply that the mix of the blended comparator needs to change over time. Please explore a scenario in which treatments that are not taken lifelong are excluded from the comparator arm at the relevant time points and provide supporting evidence.

In the base-case model, SDT is assumed to continue indefinitely. This reflects UK clinical expert input that SDT represents long-term symptom management in ISM, with patients typically remaining on some form of mix of SDT over time.^{5,24} In clinical practice, SDT regimens may be adjusted, substituted, or optimised, but this does not represent treatment discontinuation; rather, it reflects ongoing management of symptoms using the available SDT options.

By contrast, targeted therapies included within the blended comparator, most notably TKIs, are not assumed to be taken indefinitely. Consistent with clinical expert opinion and to avoid overstating long-term comparator costs or benefits, the model assumes that TKIs are discontinued after two years of use.⁵ This assumption is conservative and reflects the expectation that prolonged indefinite TKI use is unlikely in routine

ISM management, particularly in the absence of sustained benefit or due to tolerability considerations.^{5,65} This assumption is conservative and reflects the expectation that prolonged indefinite TKI use is unlikely in routine ISM management, particularly in the absence of sustained benefit or due to tolerability considerations.^{5,65}

Although some components of the blended comparator may not be used continuously as single agents (e.g. individual treatments may be stopped or switched), UK clinical experts advised that the overall SDT mix is representative of long-term management, with patients cycling between or combining therapies as needed.⁵ As such, the blended comparator reflects the average long-term treatment pattern rather than the duration of any single component in isolation.

Implementing assumptions that certain SDT components cease after a defined timepoint would require additional, highly uncertain assumptions about (i) which treatments are stopped, (ii) what therapies replace them, and (iii) whether and how symptom control changes following such adjustments. In particular, assuming cessation of SDT components without simultaneously modelling changes in symptom severity or efficacy would be clinically implausible, while modelling both treatment mix changes and associated efficacy changes would introduce substantial uncertainty not supported by robust evidence.

Therefore, the base-case approach, assuming indefinite SDT use alongside a conservative, time-limited duration for TKIs, is considered the most appropriate and transparent representation of UK clinical practice.

- i) For patients that discontinued avapritinib, treatment effect waning was assumed to occur over three months. Please justify this, also considering reasons for discontinuation. For example, if patients discontinue because of loss of effectiveness, treatment effect waning may have occurred before discontinuation.**

For patients who discontinue avapritinib, treatment effect waning was assumed to occur over three months. This assumption was informed by UK clinical expert input, who advised that loss of treatment effect following discontinuation would be

expected to occur within a 3–6 month timeframe, depending on the reason for discontinuation and individual patient characteristics.⁵

A three-month waning period was selected as a conservative assumption. Clinical experts noted that some patients may discontinue avapritinib due to loss of effectiveness, in which case waning may have begun prior to formal treatment discontinuation. In contrast, patients discontinuing for other reasons (e.g. AEs, changes in treatment strategy, or personal factors) may retain some treatment benefit for longer. Selecting the shorter end of the clinically plausible range reflects an average across these scenarios and avoids overstating the persistence of treatment benefit after discontinuation.

Overall, assuming a three-month waning period provides a cautious and clinically grounded representation of post-discontinuation symptom trajectories, consistent with expert opinion and the need to avoid overstating ongoing treatment benefit.⁵

Adverse events

B 10. The company stated that adverse events were included as a one-off event. It appears that this is the case for costs, but for the impact on health-related quality of life (HRQoL) it is unclear as the company stated in Section 3.5.5 that it is applied each cycle. Please explain your approach and potentially adjust it if it is found to lead to inconsistencies. In addition, please explain whether the duration of 14 days is sufficient for some Grade 4 events, including more severe ones recently reported in the literature (<https://pubmed.ncbi.nlm.nih.gov/39856211/>), and potentially address this using longer durations for relevant AEs in an updated model.

AE disutility is applied only in the first model cycle; the assumed duration of 14 days reflects a standard modelling approach for acute adverse events when robust, event-specific duration data are unavailable. AE costs are likewise applied as one-off events. Any statement in the CS suggesting that HRQoL impacts are applied “each cycle” does not reflect the model implementation and will be clarified to ensure consistency.

In health economic models, treatment-related AEs are commonly categorised as acute, transient events, with HRQoL impacts applied over a short duration (often a single cycle or a defined short window), unless there is strong evidence to support a longer-lasting or chronic impact. Methodological reviews and NICE economic evaluations indicate that, in the absence of reliable data on AE duration and persistence, it is appropriate to apply a short-term disutility to capture the temporary burden of experiencing an AE, rather than assuming ongoing HRQoL loss. The 14-day duration therefore represents a pragmatic average duration for acute AEs and is consistent with standard modelling practice.

The EAG has highlighted recent post-marketing evidence reporting more severe AEs. The cited FAERS disproportionality analysis (PMCID: PMC11760955) identifies neuropsychiatric AE signals and suggests that time-to-onset for some events can extend beyond two weeks. However, this evidence does not provide robust, generalisable estimates of AE duration, severity-specific HRQoL impact, or incidence, and is not specific to ISM or the licensed 25 mg dose. The authors also note inherent limitations of FAERS data, including lack of detailed clinical information and inability to infer causality or persistence. As such, this evidence does not support parameterising longer AE disutility durations in the base case.

Given these considerations, retaining a 14-day AE disutility in the base case is considered appropriate and conservative. To address residual uncertainty and test the sensitivity of results to this simplifying assumption, the company will provide a scenario analysis in which the AE disutility duration is doubled to 28 days, with all other AE inputs unchanged. This ensures that conclusions are robust to plausible longer AE durations while avoiding speculative assumptions unsupported by the evidence base.

Table 31: Scenario – Extended AE duration

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£1,774,194
Avapritinib (PAS price)	£1,100,000			£1,100,000			£1,774,194
SDT	£1,100,000	19.18	10.33				
Scenario							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£1,774,194
Avapritinib (PAS price)	£1,100,000			£1,100,000			£1,774,194
SDT	£1,100,000						

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44.

Health-related quality of life

B 11. Priority: Response adjustment. In section 3.5.3 the company stated:

“Based on Dutch clinical expert input and the definition of mild, moderate, and severe disease, it is possible for avapritinib responders (≥30% reduction in TSS) to experience clinically meaningful symptom improvement without transitioning to a less severe health state.” A utility benefit of 0.086 is thus applied to avapritinib responders.

- a) Please explain where this quote from clinical experts can be found as the EAG team could not find it in reference 97.**

The statement in CS Section 3.5.3 is not a direct quotation from reference 97 and cannot be attributed to a specific page in the advisory board document. Rather, it reflects a modelling interpretation informed by clinical expert input from both Dutch and UK clinicians.^{5,44}

Across Dutch advisory board discussions and UK clinical expert input, clinicians consistently stated that a $\geq 30\%$ reduction in TSS represents a clinically meaningful improvement in symptoms.^{5,44} Based on this, a logical modelling step was taken that patients who achieve this level of response may experience meaningful improvement in HRQoL even if they remain within the same symptom severity category, particularly among patients in the severe health state where TSS cut-offs are broad. Across Dutch advisory board discussions and UK clinical expert input, clinicians consistently stated that a $\geq 30\%$ reduction in TSS represents a clinically meaningful improvement in symptoms.^{5,44} Based on this, a logical modelling step was taken that patients who achieve this level of response may experience meaningful improvement in HRQoL even if they remain within the same symptom severity category, particularly among patients in the severe health state where TSS cut-offs are broad.

To capture this within–health state improvement, the model applies an additional utility benefit of 0.086 to avapritinib responders who do not transition to a less severe health state. This value was implemented as a pragmatic assumption of utility benefit, set at approximately half of the utility difference between the moderate and severe health states, to reflect partial benefit that is clinically meaningful but insufficient to cross a health state boundary.

This approach ensures that the model recognises clinically meaningful response consistent with clinician judgement, while maintaining transparency around the assumed magnitude of HRQoL benefit in the absence of directly observed utility data for within–health state improvements.

b) As the utility values estimated based on PIONEER (CS Table 51) also included the observations from treatment responders experiencing clinically meaningful symptom improvement without transitioning to a less severe health state, the EAG is concerned that applying an additional HRQoL improvement would likely introduce double-counting. Please justify this risk of double-counting.

The additional HRQoL adjustment applied to avapritinib responders does not introduce double-counting. The utility values estimated from PIONEER and presented in CS Table 51 reflect average health state utilities across all patients

occupying each symptom severity state at a given timepoint. As such, these utilities represent a mean value for patients in each health state and do not distinguish between patients who achieved a clinically meaningful response and those who did not, provided they remain within the same severity category.

In particular, patients in the severe health state in the SDT arm contribute to the estimated severe-state utility based on the full distribution of outcomes observed in PIONEER, including any transient or modest symptom changes that did not meet response criteria. Applying these average severe-state utilities to both treatment arms would therefore imply that severe patients in the avapritinib arm have the same HRQoL as the average severe patient on SDT, even when they have achieved a $\geq$ 30% reduction in TSS.

The additional HRQoL improvement is therefore applied to avoid under-representation of benefit, not to double-count it. It ensures that avapritinib responders who remain in the severe health state receive a higher utility than the average severe patient in the SDT arm, reflecting their clinically meaningful symptom improvement. Without this adjustment, the model would implicitly assign the same utility to severe responders on avapritinib as to non-responding severe patients on SDT, which would not reflect clinician-reported experience.

Overall, the response adjustment corrects for a structural limitation of using average health state utilities and ensures that within–health state improvements associated with treatment response are captured for avapritinib, rather than duplicating benefits already included in the PIONEER-derived utility estimates.

c) Please provide an updated economic model and scenario analysis removing the additional utility benefit applied to responders.

Table 32: Scenario – QoL benefit for severe responders excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£1,774,375
Avapritinib (PAS price)	£1,100,000			£1,100,000			£1,774,375
SDT	£1,100,000	19.18	10.33				
Scenario							
Avapritinib (list price)	£1,100,000	19.23	10.93	£1,100,000	0.06	0.59	£1,864,407
Avapritinib (PAS price)	£1,100,000	19.23	10.93	£1,100,000	0.06	0.59	£1,864,407
SDT	£1,100,000	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

B 12. Priority: HRQoL values. In section 3.3.4 the company stated: “Utility values for mild, moderate, and severe ISM were derived from EQ-5D data collected in PIONEER using the UK tariff. The utility for SSM was sourced from the Dutch Expert advisory board (2024), while the AdvSM utility was aligned with NICE TA1012 using estimates from the PATHFINDER trial (2022).”

- a) Please provide an overview per time point of the data included (i.e. the number of observations and patients at risk in mild, moderate and severe ISM), the number and pattern of missingness, and how missing data were handled.

Prior to analysis, the dataset underwent cleaning and application of inclusion and exclusion criteria, implemented in the following stepwise manner:

Step 1: Visit data for avapritinib-treated subjects were provided in duplicate in the original dataset under the labels Part 2 Baseline and avapritinib baseline efficacy. To avoid double-counting baseline observations, all Part 2 Baseline records were

excluded (rows deleted), and the avapritinib baseline efficacy baseline records were retained.

Step 2: Any visit without a complete (“good”) EQ-5D profile or TSS profile was excluded. A complete EQ-5D profile required all five EQ-5D domains to be recorded; visits with one or more missing domains were removed from the analysis dataset.

Step 3: For placebo subjects that had C7D1 (as a placebo patient) data that differed from the baseline data as a avapritinib crossover subject, the baseline data was used as the starting point for the avapritinib phase rather than the C7D1 data from the placebo phase.

No explicit imputation of missing EQ-5D or TSS data was applied in the base case. Analyses were conducted using observed data only. Cross-sectional ordinary least squares regression was used to estimate health state–specific utility values, with EQ-5D utilities regressed on TSS severity categories.

Table presents EQ-5D data availability by visit and the corresponding distribution of mild, moderate, and severe ISM among patients with both EQ-5D and TSS available.

Table 33: EQ-5D data availability by visit

Visit	Mild		Moderate		Severe		Missing responses
	Responses	Utility	Responses	Utility	Responses	Utility	
Baseline	28		53		105		1 (0.5%)
C2D1	54		57		71		5 (2.7%)
C3D1	70		41		66		10 (5.3%)
C4D1	64		49		63		11 (5.9%)
C5D1	76		48		54		9 (4.8%)
C6D1	77		46		52		11 (5.9%)
C7D1	82		53		46		3 (1.6%)
C8D1	53		35		24		63 (36.0%)
C9D1	77		43		28		24 (14.0%)
C10D1	63		23		23		59 (35.1%)
C11D1	81		35		33		17 (10.2%)

Visit	Mild		Moderate		Severe		Missing responses
	Responses	Utility	Responses	Utility	Responses	Utility	
C12D1	63		26		20		50 (31.4%)
C13D1	73		33		31		16 (10.5%)
C14D1	2		2		4		126 (94.0%)
C15D1	53		17		25		37 (28.0%)
C16D1	16		5		7		78 (73.6%)
C19D1	48		15		21		6 (6.7%)
C22D1	32		6		14		7 (11.9%)
C25D1	15		5		6		0
C28D1	8		2		3		1
C31D1	2		1		2		0
C34D1	1		0		0		0

Source: CxDx, cycle number day number; EQ-5D, EuroQoL 5-Dimension; N/A, not available.

b) Please elaborate on the risk of bias introduced by (handling of) missing data.

The primary consideration regarding missing data relates to the absence of imputation for EQ-5D and TSS values, with utility estimation based on observed data only. As utilities are estimated at the level of mild, moderate, and severe ISM health states, the potential for bias introduced by missing EQ-5D observations is limited.

TSS is a patient-reported outcome that directly reflects symptom burden and underpins health state classification.⁸⁻¹⁰ Substantial changes in HRQoL captured by EQ-5D would therefore be expected to occur alongside corresponding changes in TSS. Consequently, any potentially large changes in EQ-5D at visits with missing data would be likely to be associated with a change in symptom severity and, in turn, a change in health state. Given that utility values are derived as averages within health states rather than at the individual-visit level, unobserved EQ-5D data are unlikely to materially distort the estimated health state-specific utilities.

While missing data reduce the number of observations contributing to later visits, this primarily affects statistical precision rather than introducing systematic bias. The

observed-data approach therefore provides unbiased estimates of average utility within each health state, under the assumption that missingness is not systematically associated with utility values conditional on health state.

c) Please provide an updated model and scenario analyses using imputed data and elaborate on the method of data imputation used and the reasons it was chosen.

As a sensitivity analysis, missing EQ-5D utility observations were imputed using Last Observation Carried Forward (LOCF) methodology. LOCF was selected as a pragmatic and transparent approach that can be implemented within the Excel-based modelling framework and provides a conservative test of the impact of missing EQ-5D data on estimated utilities. In this setting, variation in EQ-5D utilities is expected to be driven primarily by between-patient heterogeneity rather than large unobserved within-patient changes over time, as meaningful changes in HRQoL would typically coincide with changes in symptom severity and corresponding health state. LOCF therefore provides a reasonable approximation for missing observations by preserving each patient's observed utility profile within a given severity context, while also equalising the contribution of patients with differing numbers of observed visits. Results from the LOCF scenario are presented to assess whether the cost-effectiveness conclusions are sensitive to the handling of missing EQ-5D observations.

Table 34: Coefficients applied with the UK tariff and the Dutch tariff

Coefficients	No imputation	LOCF
(Intercept)	██████	██████
TSS MODERATE	██████	██████
TSS SEVERE	██████	██████

Source: LOCF, Last Observation Carried Forward; TSS, total symptom score.

Table 35: Scenario – LOCF utility values

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£1,774,353
Avapritinib (PAS price)	£1,100,000			£1,100,000			£1,774,353
SDT	£1,100,000	19.18	10.33				
Scenario							
Avapritinib (list price)	£1,100,000	19.23	10.96	£1,100,000	0.06	0.61	£1,804,885
Avapritinib (PAS price)	£1,100,000			£1,100,000			£1,804,885
SDT	£1,100,000						

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44.

d) Please provide details of how the mild, moderate and severe ISM utility values were estimated. If using MMRM or a different regression approach, please include an overview of which models were considered, which candidate covariates were included, and which model was selected (including rationale)?

Mild, moderate, and severe ISM utility values were estimated using regression-based analyses applied to EQ-5D utility data collected in PIONEER. Utilities were derived using a cross-sectional ordinary least squares regression framework, with EQ-5D utility as the dependent variable and ISM symptom severity category (mild, moderate, severe, defined using TSS thresholds) as the sole explanatory variable.

No additional covariates were included in the regression models. This approach was selected to ensure direct estimation of health state-specific utilities that reflect differences in symptom severity, without introducing additional structural

assumptions or overfitting in the context of a relatively small and unbalanced longitudinal dataset with decreasing observations over time. Alternative longitudinal approaches, such as mixed models for repeated measures (MMRM), were not pursued because the objective of the analysis was to estimate mean utilities by health state rather than to model within-patient change over time, and because repeated-measures methods would require additional assumptions regarding covariance structure and missing data mechanisms that could not be robustly supported by the available data.

- e) Please provide the PIONEER utility values for mild, moderate, and severe ISM from which those presented in Table 51 are derived, as the EAG team could not find these utility values in Section , and different sources are referenced throughout the CS (e.g., on page 100 and 102 reference 15 is used but that refers to the PRISM study not PIONEER).**

The company has provided the requested supporting documentation detailing the derivation of the PIONEER utility values. This includes the statistical analysis document containing the full regression code and associated outputs used to estimate the mild, moderate, and severe ISM health state utilities from EQ-5D data collected in PIONEER using the UK tariff.⁶⁶

The document transparently reports the analytical approach, model specification, and resulting estimated utility values that underpin those presented in Table 51 of the Clinical Submission. As such, it enables full verification of the methods and results without the need to disclose patient-level EQ-5D data, which remain subject to confidentiality constraints.

- f) Please explain and justify the discrepancies in utility values presented to the Dutch Expert advisory board and the three UK clinical experts, and the utility values ultimately used in the economic model. For example, the utility value for severe ISM was 0.534 for the experts but 0.498 is used in the economic model. Similarly for SSM, 0.613 was presented to the experts and 0.531 is used in the economic model. For AdvSM, 0.519 was presented to the experts and 0.530 is used in the economic model.**

The model base-case utility value was derived and applied using the UK tariff in accordance with the NICE reference case.⁵² These UK-tariff utilities were the value communicated during the clinical expert engagement and were validated by three UK clinical experts (See Table 4. Disease category and associated utility values in the Clinical Expert Opinion Report).⁵

However, utility values presented in the Dutch Advisory Report were using UK tariff data instead of Dutch tariff.⁴⁴ Therefore, a summarised comparison of two coefficients used with different country-specific tariffs was presented in Table 36.⁴⁴ Full details and the R code used for utility mapping are provided in the statistical analysis of QoL.⁶⁶

Table 36: Coefficients applied with the UK tariff and the Dutch tariff

Coefficients	UK tariff	Dutch tariff
(Intercept)		
TSS MODERATE		
TSS SEVERE		

Abbreviations: TSS, total symptom score.

Noted that the utility value (0.498) was used in the model base case and reported in CS Table 51, which was calculated using 0.773 minus severe decrement 0.275 has now been corrected in the model, and the updated in Table 30.

Table 37: EQ-5D (PIONEER) Utility values by disease severity

Disease category	Changes in utility values	Utility values	Source
Mild			Estimate from PIONEER trial EQ-5D data. ^{3,4,28}
Moderate			
Severe			
SSM			Estimation based on the Dutch Expert Advisory Board. ⁴⁴
AdvSM			AdvSM progressed 1L, PATHFINDER trial EQ-5D data. ⁶⁷

Abbreviations: 1L, first-line; AdvSM, advanced systemic mastocytosis; EQ-5D, EuroQoL-5 Dimension; SSM, smouldering SM.

Table 38: Corrected UK tariff utility values

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)		19.23	10.95		0.06	0.62	
Avapritinib (PAS price)							
SDT		19.18	10.33				
Scenario							
Avapritinib (list price)		19.23	11.27		0.06	0.56	
Avapritinib (PAS price)		19.23	11.27		0.06	0.56	
SDT		19.18	10.71				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

g) Please explain why information from the Dutch Expert advisory board is said to be used for the SSM utility and not information from the UK clinical experts (see Appendix J/reference 44).

The SSM utility input was initially informed by the Dutch Expert Advisory Board because the company's broader evidence generation and validation activities (including PRISM-based inputs) were first discussed with that group. However, the SSM utility assumption used in the economic model was not based solely on Dutch expert opinion.

UK clinical expert engagement was subsequently conducted (Appendix J / reference 44), and the UK experts reviewed and validated the SSM utility approach and its face validity in the context of UK clinical practice. In particular, UK clinical experts validated and confirmed the appropriateness of the SSM utility assumption for the UK setting.⁵

B 13. AE disutility.

- a) Please explain why there is no disutility applied to “contusion”, “photosensitivity reaction”, and “dry mouth”.

Appreciate the EAG’s query. Disutility of “contusion”, “photosensitivity reaction”, and “dry mouth” was set to “zero” in the model base case, mainly because two reasons: 1) limited disutility data could be found on these three conditions; 2) low incidence reported in the PIONEER trial.^{28,68} Thus, these AEs are unlikely to result in a sustained reduction in HRQoL over the model cycle length when utility is already captured through the health-state EQ-5D values, which reflect overall symptom burden.^{28,68} Furthermore, these adverse events were still captured in the model through adverse event management costs, but no additional HRQoL decrement was applied.

Additionally, Table 26 of the clinical summary report (February 2025 data cut) shows that the only Grade ≥ 3 AEs that occurred in $\geq 2\%$ of the safety population were anaphylactic reactions and mast cell activation syndrome, neither of which were related to treatment.²⁸ The utility decrement related to these symptoms is assumed to have very low or zero impact on patients’ HRQoL.

Furthermore, there is evidence that xerostomia (dry mouth) and dysphagia are associated with lower EQ-5D utility, providing a coefficient of -0.336 ($p=0.006$). However, it is an adjusted effect in controlling other factors in the regression, which are not the same as “observed mean EQ-5D utilities”, so it cannot be directly used in the model.

To explore this uncertainty associated with excluding disutility for “dry mouth”, “contusion”, and “photosensitivity reaction”, the company conducted a conservative scenario analysis in which each of these AEs was assigned a fixed utility decrement of 0.05 (assumption). This scenario is included in the updated model to assess the sensitivity of the results to the ICER.

Table 39: AE disutility for contusion, dry mouth, and photosensitivity

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.097
Avapritinib (PAS price)	£19.18	19.18	10.95	£0.05	0.06	0.62	£0.081
SDT	£19.18	19.18	10.33	£0.00	0.00	0.00	£0.00
Scenario							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.097
Avapritinib (PAS price)	£19.18	19.18	10.95	£0.05	0.06	0.62	£0.081
SDT	£19.18	19.18	10.33	£0.00	0.00	0.00	£0.00

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44.

- b) Please explain the rationale of the assumption that a disutility for anxiety (0.0669) is the same as for flushing.

No published EQ-5D disutility specific to flushing in ISM was identified. Flushing is a visible, facial symptom which may lead to short-term psychosocial impact (e.g., embarrassment, distress or anxiety in social situations). In the absence of condition-specific EQ-5D estimates for flushing, the model applied a proxy disutility using the EQ-5D decrement for anxiety (0.0669) from Sullivan et al. (2011), which reports UK EQ-5D impacts for common health conditions.⁶⁹ This was implemented as a simplifying assumption to capture potential HRQoL impact from visible symptoms when direct evidence is unavailable. Therefore, the company acknowledges that this is an assumption rather than a demonstrated equivalence between flushing and anxiety,

- c) Please elaborate on the assumption that all adverse events related to oedema have a disutility of 0.1240, as the reference in CS Table 53 said this is based

on TA423 and the economic model sheet “Safety” mentioned TA250, but in both appraisals this disutility could not be found.

We acknowledge and appreciate the EAG’s observation. We re-checked TA423 (which replaced TA250) and note that neither appraisal report an oedema-specific EQ-5D disutility directly. To ensure consistent documentation, the model reference has been updated from TA250 to TA423 where relevant.

The disutility of 0.1240 for oedema-related adverse events was informed by TA627 committee paper (located in Table 44), where 0.124 was the disutility value used for pulmonary embolism, with the value ultimately traced back to disutility inputs used in the related TA423 committee paper (located in Table 55). Therefore, we took the same approach as a conservative proxy for oedema-related events.^{70,71} Figure 3 presents the source information from TA627.

Furthermore, 0.1240 was used for the oedema utility decrement, which was agreed and validated by three UK clinical experts.⁵

Figure 6: Source of oedema utility used in base case-TA627

Table 44: AE utility decrements and durations

Adverse event	Disutility	Duration (days)	Source for disutility	Source for duration
Neutropenia	0.090	15.09	Nafees et al. (2008) ¹⁴³	TA306 ¹⁴⁴
Leukopenia	0.119	13.96	TA513 ⁵² (assumed to be the same as anaemia)	TA306 ¹⁴⁴
Anaemia	0.119	16.07	Swinburn et al. (2010) ¹⁴⁵	TA306 ¹⁴⁴
Pneumonia	0.200	14.00	Beusterien et al. (2010) ¹⁴⁶	TA306 ¹⁴⁴
Lymphocyte count decreased	0.100	34.00	Stein et al. (2018) ¹⁴⁷	Assumed maximum of all Grade 3/4 AEs
Lymphopenia	0.100	34.00	Stein et al. (2018) ¹⁴⁷	TA306 ¹⁴⁴
Febrile neutropenia	0.150	7.14	Lloyd et al. (2006) ¹⁴⁸	TA306 ¹⁴⁴
White blood cell count decreased	0.100	34.00	Stein et al. (2018) ¹⁴⁷	Assumed maximum of all Grade 3/4 AEs
Diarrhoea	0.048	34.00	Nafees et al. (2008) ¹⁴³	Assumed maximum of all Grade 3/4 AEs
Thrombocytopenia	0.108	23.23	Tolley et al. (2013) ¹⁴⁹	TA306 ¹⁴⁴
Hypokalaemia	0.124	34.00	TA423 ¹⁵⁰	Assumed maximum of all Grade 3/4 AEs
Pulmonary embolism	0.124	34.00	TA423 ¹⁵⁰	Assumed maximum of all Grade 3/4 AEs
Infusion-related reaction	0.195	34.00	Tolley et al. (2013) ¹⁴⁹	Assumed maximum of all Grade 3/4 AEs
Nausea and emesis	0.048	6.00	Nafees et al. (2008) ¹⁴³	TA306 ¹⁴⁴
Allergic reaction	0.098	34.00	Hannouf et al.	Assumed

Source: NICE TA627 (2020).⁷⁰

We conducted an additional search and still did not identify a direct EQ-5D disutility estimate for “oedema peripheral” and “periorbital oedema”. However, we identified an alternative NICE appraisal that may be more directly aligned with oedema: in TA937 committee papers, “oedema peripheral” and “face oedema” were assigned a disutility of –0.16, assumed equal to “cushingoid” (See Figure 4).⁷² Therefore, the company explored –0.16 in a scenario analysis to test the sensitivity of results to a higher, oedema-specific proxy value.⁷²

Figure 7: Source of alternative oedema disutility-TA937

Table 28: Adverse event rates disutility value

Treatment-emergent AE	Disutility	Source
Acne	-0.00	Assumption
Cushingoid	-0.16	Sullivan et al. (2011) (150)
Dyspepsia	-0.04	Sullivan et al. (2011)
Oedema peripheral	-0.16	Assumed same as cushingoid
Face oedema	-0.16	Assumed same as cushingoid
Headache	-0.04	Sullivan et al. (2011) (150)
Hirsutism	-0.00	Sullivan et al. (2011) (150)
Hypertension	-0.05	Sullivan et al. (2011) (150)
Mood swings	-0.13	Sullivan et al. (2011) (150)
Upper respiratory tract infection	-0.00	Sullivan et al. 2006 (151)
Weight increase	-0.00	Assumption

Source: NICE TA937 (2025).⁷²

Table 40: AE disutility for contusion, dry mouth, and photosensitivity

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
SDT	£19.18	19.18	10.33				
Scenario							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
SDT	£19.18	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44.

- d) Please explain why “dizziness” is associated with a disutility of 0.1200 because in reference NICE CG173 0.065 was found.

The disutility applied for dizziness (0.12) was sourced from NICE CG173, Appendix F, Table F9:Model utility parameters.⁷³ As shown in Figure 5, reports a mean

absolute utility decrement for dizziness of -0.12 (SE 0.0024).⁷³ Therefore, the model uses 0.12 as the disutility for dizziness.

The value 0.065 cited by the EAG corresponds to the nausea disutility reported in the same table (CG173 Appendix F, Table F9: nausea absolute utility decrement -0.065), rather than dizziness.⁷³ Accordingly, there is no discrepancy: the dizziness disutility in CG173 is -0.12 , which is consistent with the value applied in the model.⁷³

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Additionally, 0.12 used for the dizziness utility decrement was agreed and validated by three UK clinical experts.⁵

Figure 8: Source of dizziness disutility-CG173 Appendix F

Table F9 Model utility parameters

State / event	Mean (SE)	95% CI
No pain reduction	0.16 (0.036)	0.09–0.23
30–49% pain reduction	0.46 (0.015)	0.43–0.49
50%+ pain reduction	0.67 (0.015)	0.64–0.70
Withdrawal due to adverse effects (relative utility multiplier)	0.9	0.80–0.93 (upper and lower bounds)
Dizziness (absolute utility decrement)	-0.12 (0.0024)	
Nausea (absolute utility decrement)	-0.065 (0.0013)	

Source: NICE CG173 (2013).⁷³

- e) Please explain where the disutilities for “Muscle spasms” and Anaphylaxis with(out) complications” exactly could be found in the quoted references.

1) For Muscle spasms:

The correct citation of Farkouh et al (2012) is now provided in the CQ reference pack, another publication was uploaded error. No EQ-5D disutility specific to muscle spasms was identified. Therefore, the model used a proxy decrement of 0.07 derived from preference-based standard gamble (SG) utilities for Parkinson’s health states with vs without dyskinesias (0.78 vs 0.71; decrement 0.07), as reported in Farkouh et al (2012)⁷⁴, and its ISPOR poster 2009 (See ⁷⁴Figure 6).^{74,75}

Figure 9: Source for the disutility of muscle spasms (Farkouh et al., 2009)

Utility Weights

Table 2. Health State Utility Weights³

Utilities	VAS	SG
Rasagiline	0.83	0.85
DA	0.83	0.85
DA with dyskinesias	0.63	0.76
LD without dyskinesias, as first-line treatment	0.83	0.85
LD without dyskinesias, as second-line treatment	0.72	0.78
LD with dyskinesias	0.48	0.71

SG = standard gamble; VAS = visual analogue scale.

Source: Farkouh, ISPOR poster 2009.⁷⁵

As supportive evidence, Gillard et al (2015) reported an EQ-5D index difference of -0.07 between stroke survivors with vs without spasticity. Figure 6 is a screenshot of Table 3 in Gillard et al. (2015), which shows the mean difference of utility decrement of 0.07. This provides an independent indication that a utility decrement of -0.07 is plausible for muscle spasm. The -0.07 value is therefore derived from Farkouh et al (2012) and (2009) SG utilities (not EQ-5D), and is further supported by Gillard et al. (2015) as a consistent magnitude in an EQ-5D context.⁷⁴⁻⁷⁶

Figure 10: Source for the disutility of muscle spasms-Gillard et al(2015)

HRQoL	Patients with spasticity, mean $\pm$ SE (95 % CI)	Patients without spasticity, mean $\pm$ SE (95 % CI)	Mean difference (95 % CI) ^a
SF-12			
Physical Component Summary	31.1 $\pm$ 0.9 (29.4–32.9)	37.0 $\pm$ 0.5 (36.0–38.0)	–5.8 (–7.8 to –4.0)
Mental Component Summary	50.7 $\pm$ 1.3 (48.2–53.2)	50.11 $\pm$ 0.5 (49.2–51.0)	0.6 (–2.1 to 3.2)
EQ-5D			
Index score (US weighted)	0.63 $\pm$ 0.02 (0.59–0.68)	0.71 $\pm$ 0.01 (0.69–0.73)	–0.07 (–0.12 to –0.03)
SSQOL			
Overall score	3.6 $\pm$ 0.05 (3.5–3.7)	3.8 $\pm$ 0.03 (3.8–3.9)	–0.21 (–0.32 to –0.11)

Abbreviations: CI confidence interval, EQ-5D EuroQol-5 dimension, HRQoL health-related quality of life, SF-12 Short Form-12, SE standard error, SSQOL Stroke-Specific Quality of Life, and US United States

^aAdjusted for age, race, and retrospective National Institute of Health Stroke Scale

Source: Gillard et al. (2015)⁷⁶(2015)⁷⁶

2) For anaphylaxis with(out) complications:

The correct citation of Shaker et al. (2019) is provided in the CQ reference package. The disutility of 0.09 per anaphylaxis occurrence is explicitly reported in Shaker et al. (2019).⁷⁷ In the “Immunotherapy Treatments” section, the paper states: “Health state disutility toll was applied to treatment-induced anaphylaxis (–0.09 per occurrence).”

This value is also consistent with the NICE appraisal TA769 committee papers.⁷⁸ Specifically in Tabel 58 (TA769): Disutilities due to accidental exposure to peanut and Table 59 (TA769): Disutilities due to treatment-related adverse events, both tables were derived from Carroll and Downs et al. (2009).⁷⁹

The TA769 committee paper also explicitly states the assumption that mild/moderate treatment-related anaphylactic reactions use the severe allergic reaction disutility (0.09), sourced to Carroll and Downs (2009), and that values/duration were validated by a clinical expert.

Figure 11: Source of anaphylaxis without complications (TA769)

Adverse event/reaction	Disutility	Disutility duration (days)	Total disutility
Anaphylactic reactions			
Mild anaphylactic reaction	0.09	2	0.0005
Moderate anaphylactic reaction	0.09	2	0.0005
Other adverse events			
Moderate gastrointestinal disorders*	0.07	1	0.0002
Moderate respiratory, thoracic and mediastinal disorders**	0.07	1	0.0002
Moderate skin and subcutaneous tissue disorders#	0.07	1	0.0002

TRAEE: treatment-related adverse event

* The most frequent events were: Abdominal pain, Oral pruritus, Abdominal pain upper, Nausea, Vomiting, Paraesthesia oral, Abdominal discomfort, Tongue pruritus, Lip pruritus, Lip swelling.

** The most frequent events were: Throat irritation, Cough, Throat tightness, Sneezing, Rhinorrhoea, Wheezing, Nasal congestion, Dyspnoea, Oropharyngeal pain, Pharyngeal paraesthesia.

Source: NICE appraisal TA769⁷⁸

Neither Shaker et al. (2019) nor TA769 provides a separate EQ-5D disutility specifically labelled “anaphylaxis with complications” versus “without complications. Therefore, the disutility of anaphylaxis with complications was assumed to double the utility decrement of anaphylaxis without complications.

B 14. HRQoL studies.

a) Section 3.5.2 of the CS and Appendix F mentioned that the evidence for utility was comprised of 17 unique studies out of 48 publications. Please justify this number (17) as the EAG team found 7 studies in Table 41 of Appendix F.

In table 41 in Appendix F, the dashes are also unique studies, the merged cells show the grouped publications into one study. Therefore, the 48 publications have been merged into the 17 studies as follows:

- PIONEER: N=18 publications (including the two publications from HAS and GBA)
- PRISM: N=5
- SUMMIT (NCT05186753): N=5
- NCT03770273: N=3
- Siebenhaar (2019-2023; AK002 Phase 1): N=3
- Butterfield et al (2016): N=1
- Ziegler et al (2024-2025; RWE): N=2
- Broesby-Olsen et al (2018; Omalizumab): N=1
- Van-Anrooij et al. (2016; Midostaurin phase 2): N=1
- NCT00814073 (Masitinib phase 3): N=2
- Tashi et al (2023; Elestinib [HARBOR trial]): N=1
- EUCTR (PA101): N=1
- Veitch et al. (2023; RWE): N=1
- AVATAR (RWE), Pyatilova 2025: N=1
- Mounié et al. (2025; RWE): N=1
- Van Anrooij et al. (2016; RWE): N=1
- Akin C 2024 omalizumab Treatment: N=1

b) Section 2.3.5 of the CS explained that all of these 17 identified studies were related to the PIONEER trial and therefore not included in the economic model. Please explain why NCT00814073, Ziegler 2025, Siebenhaar 2023, NCT03770273, Summit, NCT05186753 and PRISM survey are listed as separate studies in the right column of Table 41 Appendix J.

Of 48 publications screened in full-text, 17 publications were related to the pivotal PIONEER trial (NCT03731260). EQ-5D data from PIONEER was used to derive utility values hence none of these publications were used to inform the health economic model. Other studies (N=15) identified (as well as PIONEER) were not included in the health economic model due to lack of relevance to the health states being used.

Resources and costs

B 15. Priority: The EAG noted that the treatment costs for avapritinib and SDT is calculated per g/ml. Please provide an updated economic model where the treatment cost for avapritinib and oral SDTs are based on per pack basis, considering that NICE now takes a more standardised approach for modelling oral treatments to help ensure consistency of cost calculations and better reflect how treatments are dispensed in clinical practice (<https://www.nice.org.uk/process/pmg24/chapter/cost-effectiveness>).

In the submitted model, drug acquisition costs for avapritinib and oral SDTs are already derived from pack prices and the licensed dose/frequency, with costs converted to a per-cycle value to align with the monthly model cycle length. In practice, this is consistent with a “per pack” costing approach because the underlying unit cost is the pack price and the model applies the full monthly dispensed quantity implied by that pack pricing.

For avapritinib, pack presentations are aligned to monthly supply. The model therefore assumes one pack per monthly cycle while patients remain on treatment, and applies the full pack cost in the cycle in which discontinuation occurs (i.e. no pro-rating within-cycle). This reflects dispensing in clinical practice and is consistent with NICE’s standard approach for oral treatments.

For oral SDTs, the model uses the pack price and the dose/frequency to calculate the monthly quantity required and associated monthly cost. Where pack sizes do not correspond exactly to a monthly quantity, the same pack-price-based calculation results in an equivalent monthly cost over time when averaged across cycles, given SDT use is modelled as ongoing and stable within health states. As such, calculating costs “per mg” as an intermediate step does not change the underlying cost basis; it is simply a calculation method to translate pack prices into monthly per-cycle costs.

Therefore, an “updated model” using a per-pack approach would not materially change results, as the current implementation already reflects pack-based dispensing for avapritinib and oral SDTs.

B 16. Priority: Resource use. For the frequency and nature of health state unit costs for patients with ISM, also distinguishing between those patients who had different underlying levels of disease activity, the company stated in section 3.6.2 that a Dutch advisory board was consulted.

a) Please clarify how the duration of reduction in resource use for avapritinib patients responding to treatment was modelled, i.e. was it assumed to revert back to initial resource use when patients discontinued avapritinib treatment, or was it modelled until the patient died regardless of treatment discontinuation?

For patients treated with avapritinib, reductions in health state–related resource use were applied only to patients who responded to treatment and were assumed to occur from one year after treatment initiation. This timing was selected to reflect clinical practice, allowing sufficient time for treatment initiation, stabilisation, and any adjustments to SDT following improvements in symptoms.

The reduction in resource use was not assumed to persist indefinitely. For patients who subsequently discontinued avapritinib, resource use was assumed to revert to the SDT-level resource use from the cycle of discontinuation onwards. Therefore, reduced resource use is explicitly linked to ongoing treatment response and is not applied beyond avapritinib discontinuation.

b) Please explain whether this is reflective of what was observed in PIONEER and what would be expected in UK clinical practice.

The assumed reduction in resource use for avapritinib responders is not directly observed in PIONEER, as the trial was conducted under clinical study conditions with scheduled assessments and monitoring that continued regardless of symptom improvement. As such, PIONEER is not informative for changes in overall healthcare resource use over time. However, PIONEER did demonstrate a reduction in SDT use among responders, which is consistent with an expectation of reduced healthcare interactions in routine practice following sustained symptom improvement.

To inform expectations for UK clinical practice, the question of resource use reduction was discussed with UK clinical experts. Due to the abstract nature of the resource use categories presented, there was some uncertainty in interpreting the figures; however, one clinician broadly agreed with the direction and approximate magnitude of a reduction in resource use among responders (around 50%), while two clinicians did not provide a quantitative response. Importantly, no clinician suggested that resource use would remain unchanged in responders with sustained symptom improvement.⁵

More detailed discussion took place during the Dutch clinical expert advisory board, where clinicians reviewed the resource use assumptions in depth and reached consensus on the expected impact of response on healthcare utilisation.⁴⁴ The reductions agreed with the Dutch advisory board were more conservative than the initial UK assumption of a 50% reduction. Given the similarity between Dutch and UK healthcare systems, the Dutch advisory board estimates were therefore adopted in the base-case model.

The UK clinician's view that resource use would reduce in responders, with an indicative magnitude of around 50%, is explored as an optimistic scenario. Overall, the base-case approach reflects available expert consensus, aligns with the direction of effect suggested by trial evidence on SDT reduction, and adopts a conservative position in the absence of direct trial-based resource use data.

c) Please provide an updated economic model and scenario analysis capping the duration of reduction in resource use for avapritinib responders to the time on treatment (i.e. assume non-responder resource use for discontinued patients from the point of discontinuation onwards).

This scenario is not required, as it is already implemented in the base-case model. In the current model, the reduction in resource use for avapritinib responders is applied only while patients remain on avapritinib and is capped to time on treatment. When patients discontinue avapritinib, they are assumed to revert to non-responder/SDT-level resource use from the point of discontinuation onwards.

d) Please point to the correct reference as the EAG team could not find this resource use information from the Dutch advisory board in reference 97.

The resource use inputs cited by the company were informed by a secondary Dutch advisory board, rather than the primary Dutch advisory board referenced in reference 97.⁸⁰ The EAG is correct that these specific resource use assumptions are not reported in reference 97.

To address this, the company has now provided the materials from the secondary Dutch advisory board alongside the EAG questions. These advisory board materials constitute the correct source for the resource use inputs derived from Dutch clinical practice.

e) Please explain why information from UK clinical experts is not used to support assumptions regarding resource use. For example, elaborate on the discrepancy between CS Table 59 and Table 16 of Appendix J (both capturing the monthly resource use activity per health state per responder) as expert 3 mentioned that “trends are fine and look good”.

Given the uncertainty in translating clinical feedback into precise quantitative estimates of resource use, the company selected the more conservative option for the base-case resource use assumptions. It was also acknowledged that, in practice, the reduction in resource use for responders could be substantially larger; therefore, a 50% reduction in resource use was explored as a scenario to reflect a more optimistic but plausible assumption.

f) Please explain the rationale for the assumption that the monitoring costs for SSM and AdvSM are the same as for the severe health state.

The assumption that monitoring costs for SSM and AdvSM are the same as for the severe ISM health state was made based on expectations regarding the intensity and frequency of follow-up required in these populations. In the absence of robust, stratified resource use data for SSM and AdvSM, this assumption was explored with clinical experts.

Following follow-up discussions with clinical experts, clinicians advised that overall monitoring intensity would be broadly similar across severe ISM, SSM, and AdvSM.⁵

For severe ISM, monitoring is primarily driven by ongoing adjustment of SDT and management of symptoms, whereas for AdvSM monitoring focuses more on disease assessment and treatment monitoring. Although clinicians reported limited direct experience with SSM due to its rarity, they did not expect materially different monitoring requirements compared with severe ISM.⁵

On this basis, applying the same monitoring costs across these health states was considered a pragmatic and conservative assumption, avoiding the introduction of speculative differentiation in the absence of clear evidence.

g) End of life costs. In section 3.6.1 the company mentioned that they included costs associated with drug acquisition, administration, AEs, disease monitoring and end of life costs, but the latter is not included in the economic model which is explained in section 3.6.4. Please elaborate more why end of life costs are not included in the economic model and provide an updated economic model including these costs.

The reference to inclusion of end-of-life costs in Section 3.6.1 was an error in the submission text. End-of-life costs were not included in the economic model, and this is consistent with the modelling approach described in Section 3.6.4.

End-of-life costs were not included because the burden of ISM is primarily symptom-based, and no meaningful mortality differences are expected within the ISM health states. As such, including end-of-life costs for ISM would not be clinically appropriate and would not differ between treatment arms.

Mortality differences are only applied in the SSM and AdvSM health states, where disease progression is associated with increased mortality risk. Given that such a small proportion of patients progress to SSM and AdvSM, end of life cost would not materially impact the model so therefore was excluded.⁵ Therefore, we do not believe it would be an appropriate use of resources to update the model and provide an end of life cost given the incremental difference between SDT and avapritinib would be minimal, even if beneficial to avapritinib given the slightly higher rate of progression of SDT to SSM and AdvSM due to worse severity.

B 17. Subsequent treatments.

- a) In CS Table 64 the one-off costs of subsequent treatment with haematopoietic stem cell transplantation (allo-HSCT) upon progression are shown. Please provide justification for including this cost in the economic base case and provide a comparison of how allo-HSCT was modelled in other relevant NICE Tas (e.g., in TA1012 it was excluded *“based on clinical expert feedback that the rate of increased allo-HSCT eligibility and the data regarding outcomes following treatment with avapritinib and subsequent HSCT are subject to uncertainty”*.**

Allo-HSCT was included as a one-off subsequent treatment cost upon progression because, for patients who progress to AdvSM, allo-HSCT is a clinically relevant, expensive and resource-intensive treatment option and therefore represents a plausible downstream NHS cost consequence of progression. Clinical input used to inform the AdvSM avapritinib modelling work indicated that allo-HSCT would be expected in approximately 10% of AdvSM patients, consistent with eligibility expectations discussed previously in NICE guidance for avapritinib in AdvSM (TA1012).⁵ The key uncertainty relates to how prior treatment with avapritinib may influence subsequent eligibility for, timing of, and outcomes following allo-HSCT, rather than uncertainty around the use of allo-HSCT itself.

- b) The EAG team found that avapritinib is also indicated as monotherapy for patients with AdvSM from the SmPC. Please justify whether patients progressing to AdvSM are subsequently treated with avapritinib. If not yet included, please provide an updated economic model where costs related to subsequent avapritinib treatment are included for patients who progress to AdvSM.**

DoT was taken from the median DoT from the AdvSM model (NICE TA1012), where the median DoT for the parametric curves were 42 months for avapritinib (applied as a one-off cost upon entering the AdvSM state).⁵⁹

Table 41: Scenario – Avapritinib as a subsequent treatment for AdvSM

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
SDT	£19.18	19.18	10.33				
Scenario							
Avapritinib (list price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
Avapritinib (PAS price)	£19.23	19.23	10.95	£0.06	0.06	0.62	£0.09
SDT	£19.18	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44.

c) Please explain whether other subsequent treatments may be relevant in either treatment arm and provide an updated economic model and scenario analysis including these.

Other subsequent treatments may be relevant following progression to AdvSM. In particular, midostaurin is an alternative first-line treatment option to avapritinib for AdvSM that may be used in clinical practice. There is, however, uncertainty regarding how midostaurin and avapritinib will be positioned relative to each other as first-line AdvSM treatments over the modelled time horizon, given the recent availability of avapritinib in the UK and the lack of established long-term real-world sequencing data.

To reflect this uncertainty, a scenario can be explored in which, upon progression to AdvSM, patients receive a 50/50 split between avapritinib and midostaurin as first-line AdvSM treatment. Time on treatment assumptions for both therapies would be informed by the rates applied in TA1012 (42 months for avapritinib and 13 months for midostaurin), applied consistently across treatment arms.⁵⁹ This scenario allows

assessment of the potential impact of alternative first-line AdvSM treatment use without making strong assumptions regarding future uptake or sequencing patterns.

Table 42: Scenario – Avapritinib and midostaurin as a subsequent treatment for AdvSM

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£17,743,750
Avapritinib (PAS price)	£1,100,000			£1,100,000			£17,743,750
SDT	£1,100,000	19.18	10.33				
Scenario							
Avapritinib (list price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£17,743,750
Avapritinib (PAS price)	£1,100,000	19.23	10.95	£1,100,000	0.06	0.62	£17,743,750
SDT	£1,100,000	19.18	10.33				

Abbreviation: LYG: Life-years gained; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme

Note, these scenarios are applied to the submission model. The scenario results adapted for the adjusted model including model fixes can be found in Table 44

- d) The company stated in the UK primary research report that “*It is assumed in the model that 50% of ISM patients are retreated with SDT as subsequent treatment following discontinuation of avapritinib*”. Please provide justification for this assumption and provide an updated economic model and scenario analyses including 100% retreatment with SDT as subsequent treatment for avapritinib discontinuers.**

The statement that 50% of patients are retreated with SDT following discontinuation of avapritinib relates to an assumption in an earlier global model. This assumption was not retained in the current UK submission model.

In the current version of the model submitted to NICE, patients who discontinue avapritinib are assumed to move to SDT as subsequent treatment with a 100%

retreatment rate. Therefore, the EAG request for an updated model and scenario including 100% retreatment with SDT is already implemented in the base case, and no additional update or scenario is required.

B 18. Discrepancies between the CS and the economic model

- a) Please explain the discrepancy between CS Table 60 and the economic model sheet “RU and indirect costs” as the costs for some resource activities differ significantly (e.g., Skin domain: Dermatologist nurse visit, Accident and Emergency visit, Hospitalisation, Daycase admission, Anaphylaxis with(out) complications, Bone marrow biopsy, ECG, Coagulation test, Phototherapy, and Full blood count)**

We acknowledge and appreciate the EAG’s observation. The discrepancy between CS Table 60 and the economic model sheet “RU and indirect costs” due to an outdated version of the table was inadvertently retained in the CS.

The economic model sheet “RU and indirect costs” contains the correct and final unit costs applied in the base case. To resolve this, Table 43 is provided as a replacement for CS Table 60, fully aligned with the inputs used in the submitted model.

Table 43: Healthcare resource consumption and costs

Resource use activity	Unit cost	Reference
Abdominal pain	£129.43	Non-consultant-led outpatient (£129; PSSRU 2024/25) + paracetamol 500 mg × 4 (eMIT 2024–25); PSSRU unit cost drawn on NHS England’s National Cost Collection 2023/2024
Nausea	£182.00	NICE TA728(£182)(2020). https://www.nice.org.uk/guidance/ta728/evidence/appraisal-consultation-committee-papers-pdf-9256414285 , based on TA400
Diarrhoea	£182.00	NICE TA728(£182)(2020). https://www.nice.org.uk/guidance/ta728/evidence/appraisal-consultation-committee-papers-pdf-9256414285 , based on TA400
Brain fog	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Dizziness	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Headache	£129.43	Non-consultant-led outpatient (£129; PSSRU 2024/25) + paracetamol 500 mg × 4 (eMIT 2024–25)

Resource use activity	Unit cost	Reference
Flushing	£129.00	Non-consultant-led outpatient (£129; PSSRU 2024/25)
Itching	£133.93	Non-consultant-led outpatient (£129; PSSRU 2024/25) + hydrocortisone 1% cream 15 g (eMIT 2024–25)
Spots	£133.93	Non-consultant-led outpatient (£129; PSSRU 2024/25) + hydrocortisone 1% cream 15 g (eMIT 2024–25)
Gastrointestinal domain: outpatient consultation	£175.00	National costs collection for NHS 2023/24, Gastroenterology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 301)
Skin domain: Dermatology outpatient consultation	£164.00	National costs collection for NHS 2023/24, Dermatology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 330)
Skin domain: Dermatologist nurse visit	£118.00	National costs collection for NHS 2023/24, Dermatology Service (Total Outpatient Attendance) - Average cost of Non-Consultant-led (Service code 330)
Neurologic domain: outpatient consultation	£249.00	National costs collection for NHS 2023/24, Neurology Service (Total Outpatient Attendance) - Average cost of Consultant-led (Service code 400).
Accident & Emergency visit	£273.00	Emergency care (£273; PSSRU 2024–25)
Hospitalisation	£2,963.00	Average of Non-Elective Long/Short stay Hospitalisation (£5134/£792; PSSRU 2024–25)
Daycase admission	£1,031.00	Day cases (£1,031; PSSRU 2024–25)
Anaphylaxis without complications	£1,364.69	Anaphylaxis without complications (assumed EpiPen tried but did not work (£60.69; BNF 2025), A&E visit (£273; PSSRU 2024–25), and day case (£1,031; PSSRU 2024–25)
Anaphylaxis with complications	£4,930.69	Anaphylaxis with complications (assumed EpiPen tried but did not work (£60.69; BNF 2025), critical care (£1,907; PSSRU 2024–25), and Hospitalisation (£2,963; PSSRU 2024–25)
EpiPen use	£60.69	Cost of EpiPen (300mcg) and ampoule of adrenaline (BNF 2025)
Bone marrow biopsy	£452.00	National schedule of reference costs Total HRG 2023/24: Diagnostic Bone Marrow Extraction (SA33Z)
ECG	£108.00	National schedule of reference costs 2023/24: RD51A - Simple Echocardiogram, 19 years and over
Haematology visit	£195.00	National schedule of reference costs 2023/24: Outpatient Attendances Data: 303- Clinical haematology, consultant lead
Biochemistry test: renal - Urea and	£4.00	National schedule of reference costs 2023/24: PATH04 - Urology service

Resource use activity	Unit cost	Reference
electrolytes test (UE test)		
Coagulation test	£7.00	National schedule of reference costs 2023/24: PATH05- Clinical Haematology service
Serum chemistry tests	£1.00	National schedule of reference costs 2023/24: PATH04 - Chemical Pathology service
Phototherapy	£218.00	National schedule of reference costs 2023/24: JC47Z - Phototherapy or Photochemotherapy (Clinical haematology service)
CT scan	£115.00	National schedule of reference costs 2023/24: Average of RD20A
Chest X-ray	£78.00	National schedule of reference costs 2023/24: RD97Z - Same day Diagnostic Imaging admission or attendance
Ultrasound scan	£65.00	National schedule of reference costs 2023/24: Average of RD40Z -Ultrasound Scan with duration of less than 20 minutes, without Contrast
MRI scan	£162.00	National schedule of reference costs 2023/24: Average of RD01A -Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
Full blood count	£7.00	National schedule of reference costs 2023/24: PATH05- Clinical Haematology service
Bone densitometry	£78.00	National schedule of reference costs 2023/24: Average of RD50Z - DEXA Scan

Abbreviations: A&E, accident and emergency; eMIT, electronic market information tool; GP, general practitioner; PSSRU, Personal Social Services Research Unit. A&E, accident and emergency; CT, computerised tomography; ECG, electrocardiogram.

Source: PSSRU (2024/2025)⁸¹; British National Formulary⁸²; eMIT database⁶⁰ PSSRU unit cost drawn on NHS England's National Cost Collection 2023/2024, all costs inflated to 2024/2025.

- b) Please explain the discrepancy between CS Table 62 and the economic model sheet "RU and indirect costs" showing the summarised disease health state costs per responder and non-responder.

We acknowledge and appreciate the EAG's observation. This discrepancy has the same underlying cause as in B18(a), CS Table 62 was calculated based on the unit costs and resource use inputs presented in Table 60 (replaced by Table). Because CS Table 60 was not updated to reflect the final unit costs implemented in the economic model, the calculated responder and non-responder health-state costs reported in CS Table 62 are also inconsistent with the values shown in the model sheet "RU and indirect costs".

The model sheet “RU and indirect costs” contains the correct and final unit costs applied in the base case. To address this, Table is provided as a replacement for CS Table 62, fully aligned with the inputs used in the submitted model.

Table 44: Costs for disease health states by TSS

Resource use costs per cycle	Mild	Moderate	Severe
Non-responder			
Responder			

Abbreviations: TSS, total symptom score.

B 19. AE-related costs.

- a) Please provide cross-validation for the AE-related cost values in CS Table 65 with other NICE appraisals. For example, Oedema peripheral, Periorbital oedema, Eyelid oedema, and Face oedema are all associated with a cost of £46.99 (Bumetanide drug used to treat, BNF price (£2.29) + 10 mins GP visit based on PSSRU (10*£4.47)), whereas in TA1012 Unspecified oedema is associated with a cost of £702 (WH10A, WH10B).

The AE-related costs in CS Table 65 were cross-validated against costs used in other NICE appraisals where comparable AE management assumptions were available. In particular, the unit costs for nausea (£182), diarrhoea (£182) and fatigue (£91.68) were aligned to those reported in TA728 committee papers (Table 58), which in turn referenced costs adopted in earlier NICE appraisals.⁵³

The EAG noted that TA1012 applies a substantially higher cost for “unspecified oedema” (£702; HRG codes WH10A/WH10B from 2021/2022 national cost collection).^{59,83} In contrast, the oedema events modelled in the CS are costed assuming typical low-frequency and low-grade oedema management; Table 26 of the clinical summary report (February 2025 data cut) shows that the only Grade ≥3 AEs that occurred in ≥2% of the safety population were anaphylactic reaction and mast cell activation syndrome, neither of which were related to treatment.²⁸ Therefore, primary-care consultation plus symptomatic treatment would better reflect these AE costs listed in CS Table 65, rather than a hospital-coded inpatient cost. Anaphylaxis costs were captured in the resource unit costs. To avoid double-counting, the AE costs did not include the cost of anaphylaxis management.

- b) Please explain the rationale for the assumption that there are zero costs for four AEs (“flushing”, “hair colour changes”, “photosensitivity reaction”, and “dizziness”).

Appreciate the EAG’s question. Table 26 of the clinical summary report (February 2025 data cut) shows that the only Grade ≥ 3 AEs that occurred in $\geq 2\%$ of the safety population were anaphylactic reactions and mast cell activation syndrome, neither of which were related to treatment.²⁸ In contrast, events such as flushing, hair colour changes, photosensitivity reaction and dizziness were generally reported as lower-grade and would typically be managed with reassurance, self-care and/or routine symptomatic measures rather than requiring specific prescribed treatment, GP visits, or secondary-care management. As a result, these events are expected to incur minimal incremental NHS costs, and a zero-cost assumption was applied in the base case to avoid introducing unsupported cost assumptions.

This approach is consistent with precedent in relevant NICE appraisals.⁵² For example, in TA1012 (AdvSM), the economic analysis focused on Grade ≥ 3 adverse events.⁵⁹ In the current submission, the company adopted a more conservative approach by including the most common AEs ($\geq 10\%$ incidence) irrespective of grade;²⁸ however, for the four events listed above, no routine NHS management costs were applied because their management is expected to be minimal in most cases.

Severity

B 20. In section 3.7 the company stated: “Based on the model results, the discounted QALY outcome (at 3.5%) for SDT was 10.33, compared with 17.7 when undiscounted. Table 66 presents the QALY shortfall based on the base case result. Using the model’s starting age of 40 years and a 73% female proportion, the absolute QALY shortfall was estimated at 8.35 (discounted) and 24.84 (undiscounted), corresponding to proportional shortfalls of 44.69% and 70.63%, respectively, via the validated QALY shortfall calculator.”

- a) Please explain how the 24.84 (undiscounted) absolute QALY shortfall was calculated, as the EAG team calculated $35.17 - 17.7 = 17.47$.

The undiscounted absolute QALY shortfall value of 24.84 reported in the CS was calculated in error. The correct calculation of undiscounted absolute QALY shortfall is the difference between the undiscounted general population QALYs (35.17) and the undiscounted QALYs for SDT (17.70), which equals 17.47. We agree with the EAG's calculation ($35.17 - 17.70 = 17.47$).

- b) Please explain why the “reference case: MHV value set + HSE 2014 ALDMMM model” seem to be selected in the QALY shortfall calculator and not “alternative A: 5L to 3L mapping (Hernandez Alava et al) + HSE 2017-2018” in line with **NICE DSU TSD 23**.

Using the NICE QALY shortfall calculator with Alternative A: 5L to 3L mapping (Hernandez-Alava et al.) + HSE 2017–2018, the revised shortfall estimates are as follows.⁸⁴

For the undiscounted analysis, remaining general population QALYs at age 40 with 73% female are 33.86, while undiscounted QALYs with the disease (SDT) are 17.70, resulting in an absolute QALY shortfall of 16.16 and a proportional shortfall of 47.72%.

For the discounted (3.5%) analysis, remaining general population QALYs are 17.84, while discounted QALYs with the disease (SDT) are 10.33, resulting in an absolute QALY shortfall of 7.51 and a proportional shortfall of 42.09%.

These results replace the previously reported values in the CS, which were affected by both a calculation error and the use of a non-preferred calculator setting. The updated estimates are consistent with NICE DSU TSD 23 and will be reflected in the revised submission tables and narrative.

Company's sensitivity analyses

B 21. Deterministic sensitivity analysis. (DSA)

- a) Please elaborate on the following unclarities related to the DSA:

- i. Please explain why in the economic model sheet “DSA trace” the trace stops after row 476.

In the economic model, the DSA trace sheet was originally configured to capture a predefined set of model parameters. Subsequently, additional parameters were added to the model, primarily related to adverse events. However, the existing DSA trace formulae were not extended to include these newly added rows, which is why the trace stops after row 476.

The parameters beyond this point are largely adverse-event–related inputs and do not materially influence the ICER. As a result, they do not feature among the most impactful parameters in the deterministic sensitivity analysis, and their exclusion from the DSA trace does not affect the conclusions drawn from the DSA results.

For completeness and transparency, the DSA trace formulae has been updated in a revised model version to ensure that all parameters, including those added after row 476, are captured, although this is not expected to change the DSA outcomes or the overall cost-effectiveness conclusions.³⁹

- ii. Please explain why various utility parameters (e.g. 18 utility, 19 utility, caregiver disutility) were included in the DSA of which the use in the economic model is unclear

All parameters that are potentially suitable for deterministic sensitivity analysis were included in the DSA parameter list as part of a comprehensive and standardised DSA setup, regardless of whether the corresponding functionality was active in the base-case model at the time of submission. This includes several utility parameters (e.g. caregiver disutility) for which the associated model switches were set such that they were not applied in the base case.

As a result, although these parameters appear in the DSA, varying their values does not lead to changes in model output because the relevant calculations are not active. Their inclusion in the DSA parameter list therefore does not indicate that they influence the base-case results; rather, it reflects a generic approach to DSA specification that allows parameters to be readily activated and tested in future scenario analyses.³⁹

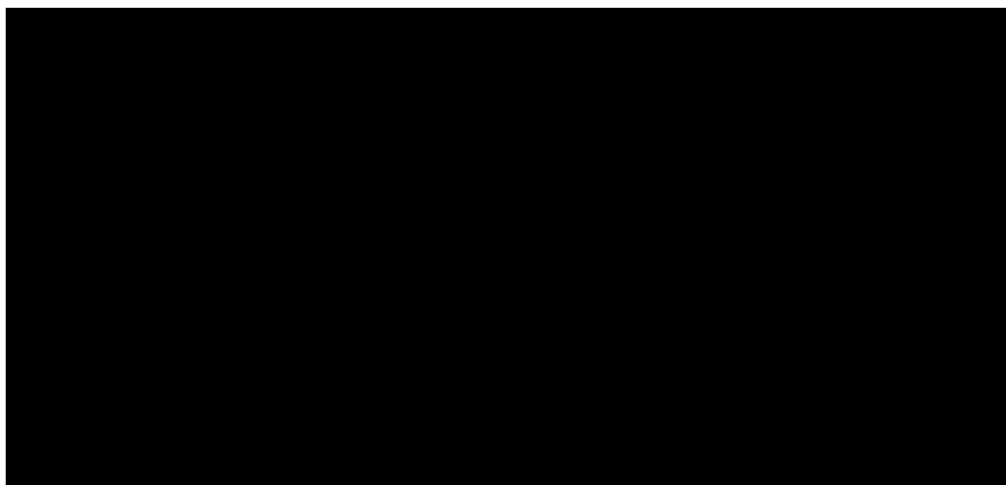
- iii. Please explain why various parameters (e.g., avapritinib and SDT proportion of patients in cycles) were included in the DSA but not varied i.e., lower and upper limit are the same as the original value

Some parameters, such as the proportions of patients on avapritinib or SDT by cycle, were included in the DSA parameter list for completeness but were not varied because they are structurally interdependent with other model components, in particular health state occupancy and treatment allocation logic. Varying these parameters independently would risk creating internally inconsistent or infeasible model states (e.g. proportions not summing to one or misalignment between treatment and health state distributions).

To avoid introducing such impossible scenarios and additional structural complexity, the lower and upper bounds for these parameters were set equal to the base-case value, effectively excluding them from variation in the DSA. Their inclusion in the parameter list therefore does not imply that uncertainty around these values was ignored; rather, uncertainty in treatment use and health state distribution is captured elsewhere in the model through clinically meaningful scenario analyses and the probabilistic sensitivity analysis.

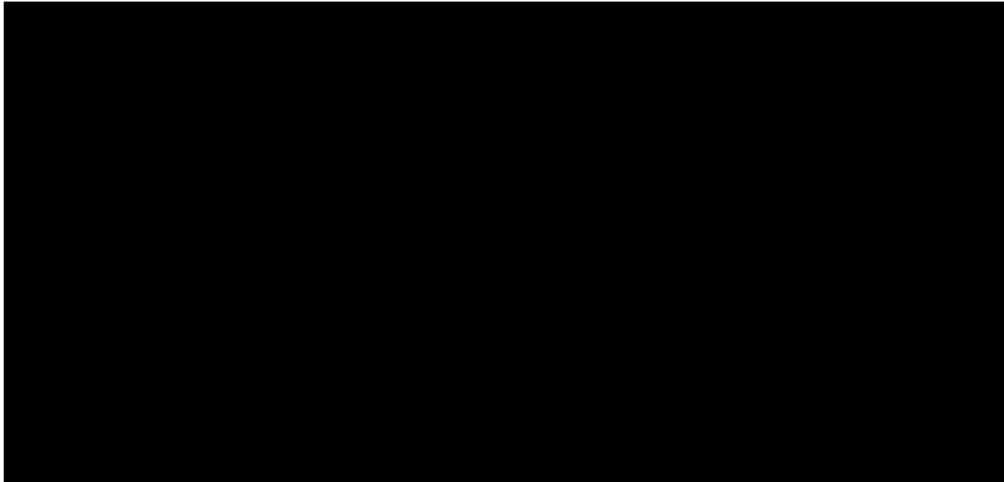
- b) To verify the results stated in section 3.11.2.1. Please enable Tornado diagrams in the economic model sheet “DSA” without PAS, and with incremental ICURs as reported in CS Figure 23 and 24.

Figure 12: DSA ICUR with PAS



Abbreviations: DSA, deterministic sensitivity analysis; incremental cost-utility ratio; PAS, patient access scheme; SDT, symptom-directed therapy.

Figure 13: DSA ICUR without PAS



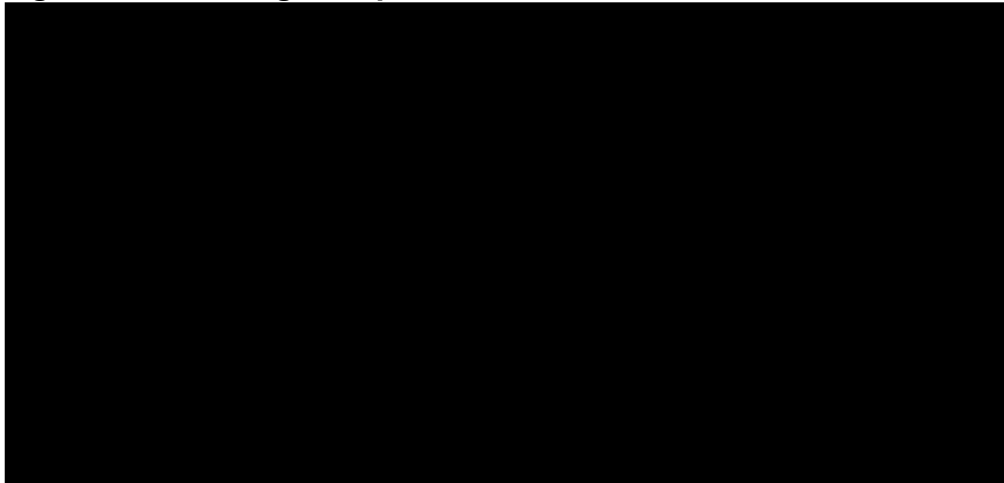
Abbreviations: DSA, deterministic sensitivity analysis; incremental cost-utility ratio; PAS, patient access scheme; SDT, symptom-directed therapy.

B 22. PSA. In section 3.9.1 The company mentioned that “a probabilistic sensitivity analysis (PSA) was performed for the base case to account for joint uncertainty across parameters.”

- a) “The base case PSA was run for 1,000 iterations, which was sufficient to achieve stable and reproducible results.” Please justify why 1,000 iterations seemed sufficient with convergence plots.

The base-case PSA was run for 1,000 iterations to ensure stable, reproducible results while maintaining computational efficiency in the Excel-based model. Convergence was assessed using convergence plots (e.g., running mean estimates of total costs, total QALYs, and incremental outcomes), which showed that results stabilised and reached a clear plateau after ~350 iterations, with only minor stochastic fluctuation thereafter. On this basis, 1,000 iterations provides a substantial margin beyond the point of convergence, reducing Monte Carlo error further and ensuring that the reported mean ICER and CEAC results are robust to simulation noise.

Figure 14: Convergence plot for INMB



Abbreviations: INMB, Incremental Net Monetary Benefit.

- b) The company stated: “All parameters were included in the PSA, except for time horizon, discount rates and drug costs, as these are considered policy-driven or fixed inputs rather than stochastic variables.” However, the EAG noted that input parameters such as “TSS response rate: avapritinib” and “avapritinib early discontinuation rate” were also not included in the PSA. Please provide an updated economic model and PSA including all inputs not considered policy driven or fixed.

In the submitted base-case PSA, parameters were excluded where they were policy-driven or fixed (time horizon, discount rates and drug acquisition costs). The EAG correctly noted that some additional parameters (including “TSS response rate: avapritinib” and “avapritinib early discontinuation rate”) were not stochastically sampled in the PSA as implemented.

For TSS response rate, this was not sampled as a standalone PSA input because response is not used as an independent driver in the model; instead, response is operationalised through the empirically observed avapritinib and SDT health-state occupancy distributions (mild/moderate/severe over time), and uncertainty is therefore captured via the PSA sampling applied to those health-state proportions (Dirichlet distributions). As such, sampling a separate “TSS response rate” parameter would risk double-counting uncertainty (once through response and again through health-state occupancy), while not changing model outputs in a structurally coherent way.

For avapritinib early discontinuation, this parameter should be treated as stochastic (i.e., not policy-driven/fixed). An updated version of the model will therefore include early discontinuation in the PSA (sampled using the specified distribution), ensuring that uncertainty in early discontinuation is propagated jointly alongside other uncertain parameters.

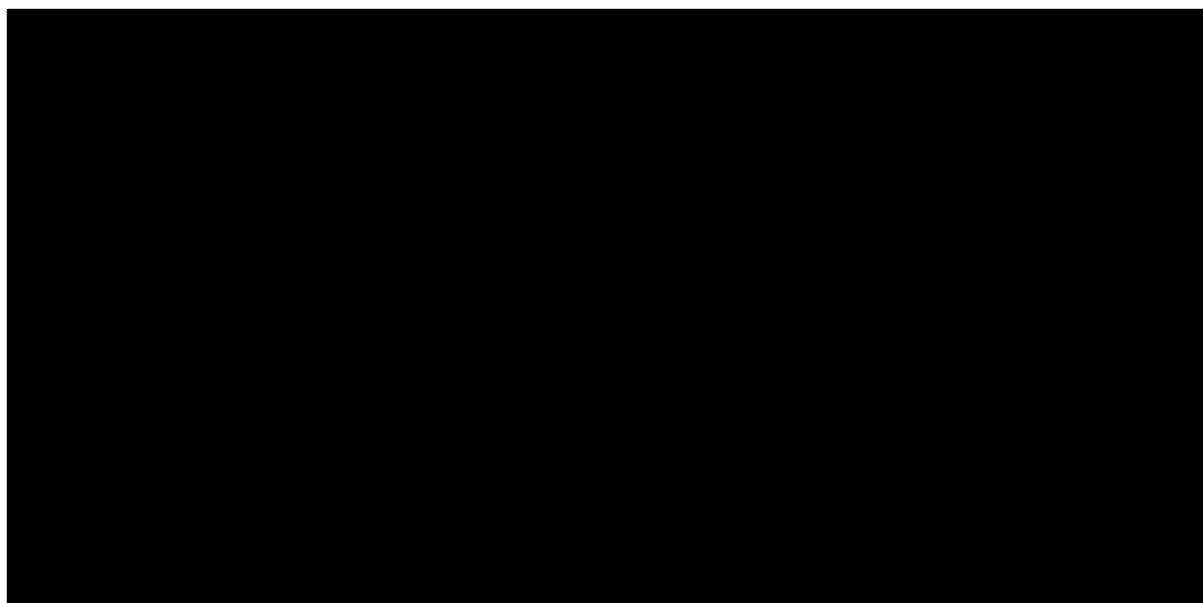
In addition, the PSA parameter list will be reviewed and updated to ensure that all non-policy/fixed inputs are included, and that distributions are aligned with parameter type (e.g., beta for probabilities/utilities, gamma for costs, lognormal for ratios/time-to-event-type parameters, and Dirichlet for multinomial health-state proportions). Any parameters currently marked as included but not sampled (or sampled but not used) will be corrected for consistency between the PSA settings and the model implementation.

Table 45: PSA including additional parameter variations

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Probabilistic results					
Avapritinib (PAS price)	██████████	9.818	██████████	0.520	██████████
SDT	██████████	9.298			

Abbreviation: ICER, incremental cost-effectiveness ratio; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis.

Figure 15: Incremental costs and QALYs of avapritinib vs comparators



Abbreviations: QALY, quality-adjusted life-year; SDT, symptom-directed therapy.

- c) For probabilistic analyses, utility and probability parameters are usually assigned a beta distribution, cost parameters a gamma distribution, and ratios a log-normal distribution. Please provide justification for all parameters for which a different distribution was selected and correct if deemed appropriate.

For PSA, distributions were assigned based on parameter type and standard health economic practice. Parameters not included in PSA (Include=FALSE) are held fixed and therefore their distribution entries do not affect PSA results. Among parameters included in PSA (Include=TRUE), probabilities and utilities were modelled using beta distributions, costs using gamma distributions, and ratios/time-to-event-type parameters using log-normal distributions. Where a set of proportions must sum to one (e.g., health state occupancy proportions), Dirichlet distributions were used to preserve the multinomial structure and ensure sampled values remain coherent (non-negative and summing to one).

Following a full review of the PSA parameterisation, all included parameters have been aligned appropriately with these conventions throughout the model. Any instances where a distribution label was inconsistent with the underlying parameter type have been corrected in the updated model so that (i) bounded parameters remain bounded under sampling, (ii) sampled values remain clinically and

mathematically plausible, and (iii) the PSA implementation is consistent with how parameters enter the calculations.

B 23. Scenario analyses.

- a) The EAG team was unable to replicate the deterministic base case results for scenario analyses “Wane after 6 months”, “starting age: 51” and “starting age: 36” shown in Table 81. Please provide a more detailed description to facilitate implementation in the health economic model. In addition, please provide a separate sheet in the health economic model where all scenarios, including those in response to the clarification letter, can be easily implemented.
- b) Please explain why there is a scenario called “SSM utility 0.663”, whereas the economic model sheet “Inputs” shows this SSM utility seems to be changed to 0.613 instead of 0.663.

We acknowledge and appreciate the EAG observation. The scenario label “SSM utility 0.663” was a naming typo. The underlying input value applied in the model for this scenario is 0.613, and the scenario name has been corrected to “SSM utility 0.613” in the updated model.

The value 0.613 is sourced from the PRISM study, which reported a mean (range) EQ-5D index score of 0.613 (0.147-1.0) for patients with SSM.²⁰

In the base-case analysis, both Dutch and UK clinical experts advised that SSM patients is likely associated with lower health-related quality-of-life, and that utility may be closer to the ISM severe health state. Therefore, the base case uses expert-informed utility assumptions for SSM.^{5,44} This scenario analysis was included to test the sensitivity of the ICER to using the PRISM mean utility value 0.613 for SSM, which is higher than the base-case SSM utility value, and to assess the impact of this alternative assumption on cost-effectiveness results.^{5,44} This scenario analysis was included to test the sensitivity of the ICER to using the PRISM mean utility value 0.613 for SSM, which is higher than the base-case SSM utility value, and to assess the impact of this alternative assumption on cost-effectiveness results.

Validation

B 24. In the CS, it was stated that “Comprehensive quality-control procedures were undertaken to ensure the accuracy and integrity of both the model simulation and its conceptual implementation”. Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, <https://pubmed.ncbi.nlm.nih.gov/31705406/>) and provide the results.

Please see supplementary file: ID6578_TECH-VER_avapritinib_20Jan2026 (sent along with this CQ response document) which details the completed TECH-VER checklist for our cost-effectiveness model.

B 25. Please provide cross validations, i.e. comparisons with other relevant NICE TAs focused on similar, potentially relevant, diseases (e.g. related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

a) Model structure and assumptions

b) Input parameters related to:

i. Clinical effectiveness

ii. Health state utility values

iii. Resource use and costs

c) Estimated (disaggregated) outcomes per treatment option:

i. Life years

ii. QALYs

iii. Costs

There are no directly comparable published NICE TAs with a sufficiently similar decision problem to support meaningful cross-validation of the CEM for avapritinib in ISM. ISM is a rare condition with a symptom-driven treatment goal, and the submitted model is structured around symptom severity (mild/moderate/severe) with

progression to SSM/AdvSM, reflecting the endpoints and disease characterisation used in PIONEER and clinical practice. The most closely related NICE appraisal in mastocytosis concerns avapritinib in AdvSM (TA1012)⁵⁹, but the decision problem, population, outcomes, and treatment objectives differ materially (disease modification and survival in AdvSM vs symptom control in ISM), limiting the relevance of direct cross-validation.

Given the absence of relevant TAs for a like-for-like comparison, external validation focused on clinical plausibility and alignment with UK practice. Model structure and key assumptions (including symptom-based health states, response implementation, discontinuation assumptions, SDT use, and resource use patterns) were validated through UK clinical expert input, supported by additional clinician discussions where relevant.^{5,24} This provides assurance that the model reflects expected clinical pathways and management in the NHS.

For input parameters, clinical effectiveness and health state occupancy were derived from PIONEER, with supporting assumptions informed by clinical expert input where evidence was limited. Utilities were estimated using trial-derived data and applied consistently by health state, with additional response adjustments implemented to reflect clinically meaningful within–health state improvement where appropriate. Resource use and costs were informed by expert input and standard NHS costing sources; where uncertainty existed, conservative assumptions were selected and explored in scenario analyses.

Finally, because there are no comparable NICE models in similar populations with the same outcome framework, it is not possible to provide a robust cross-validation of disaggregated outcomes (life years, QALYs, and costs) against external TAs. The submission instead presents internal validation (model debugging and coherence checks) and clinical validation (expert review of trajectories, plausibility of state occupancy and costs), which is the most appropriate approach given the lack of directly comparable NICE appraisals.

B 26. Further external validation of modelled effectiveness would be desirable.

a) Please report on the face validity of the model structure, modelling assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).

i. Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using

ii. evidence used to develop the economic model.

iii. evidence not used to develop the economic model.

The face validity of the model structure, key assumptions, inputs, intermediate outcomes, and final outcomes was assessed through a combination of evidence-based review and structured clinical expert input, reflecting the limited availability of external comparators in this rare disease setting.

The model structure was assessed for clinical plausibility and relevance to UK practice. The use of symptom severity–based health states (mild, moderate, severe ISM), with progression to SSM and AdvSM, was reviewed and confirmed by UK clinical experts as an appropriate representation of disease management in ISM, where the primary treatment objective is symptom control rather than disease modification.^{5,24} The implementation of treatment response, stopping rules, and treatment discontinuation assumptions was assessed to ensure consistency with how avapritinib and SDT are expected to be used in routine practice. Experts considered the structure to be appropriate and reflective of clinical pathways observed in the NHS.⁵

Model inputs were assessed against the evidence used to develop the economic model. Clinical effectiveness inputs, including health state occupancy over time, were derived directly from PIONEER and were reviewed for consistency with trial findings and expected symptom trajectories. Adverse event rates and discontinuation patterns were informed by PIONEER where available and were judged to be clinically plausible. Duration of treatment represents a key area of uncertainty, reflecting the immaturity of long-term follow-up in PIONEER and the heterogeneity observed in external data sources; however, the base-case ToT assumption was

informed by UK and international KOL input and validated as clinically reasonable for routine practice.^{5,44} Utility values for mild, moderate, and severe ISM were derived from EQ-5D data collected in PIONEER and applied consistently by health state, aligning HRQoL outcomes with symptom severity. Resource use patterns and SDT treatment mix were informed by trial data, where available, and supplemented by expert input to reflect UK practice.^{5,44,80} Cost inputs were sourced from standard UK references (e.g. NHS reference costs, PSSRU), supporting their external validity in the NHS context. Mortality assumptions were derived from published literature and reviewed with clinicians to ensure plausibility for the ISM population.

Intermediate outcomes were assessed primarily against the evidence used to develop the model rather than against external quantitative benchmarks. Where intermediate outcomes were derived directly from PIONEER (notably health state occupancy over time), these were considered internally valid by construction, as they directly reflect observed trial data and the symptom-severity framework underpinning the model. Other intermediate outcomes, including treatment persistence, HRQoL by health state, and resource use trajectories, were reviewed for internal coherence and clinical plausibility in light of the model structure and assumptions. Given the lack of external datasets capturing comparable symptom-based pathways in ISM, no independent quantitative sources were available to formally validate these intermediate outcomes. Clinical expert review therefore focused on whether the direction and relative magnitude of effects under avapritinib versus SDT were consistent with expected symptom improvement, stability or improvement in severity distribution, and downstream implications for HRQoL and healthcare use.^{5,24}

Final outcomes (life years, QALYs, and costs) were similarly assessed for plausibility rather than external numerical comparison, as there are no published NICE models or real-world studies reporting comparable outcomes in an ISM population using a symptom-severity framework. Life years were not expected to differ materially between treatments in ISM and were not a key driver of results. Review therefore concentrated on whether the incremental QALYs and costs were directionally and proportionally consistent with the modelled improvements in symptom burden, health state occupancy, HRQoL, and resource use. In the absence of valid external

comparators, the consistency between trial-derived intermediate outcomes and modelled final outcomes was considered the most appropriate form of validation.

Overall, the face validity assessment concluded that the model structure, assumptions, inputs, intermediate outcomes, and final results are clinically plausible and externally valid for the NHS decision context. While formal quantitative validation against external models is not feasible due to the lack of comparable NICE appraisals, the combination of trial evidence, standard UK data sources, and expert validation provides reassurance that modelled effectiveness and outcomes are appropriate and credible.

Scenario results (adapted model)

Table 46: Scenario results for adapted model (PAS price)

Scenario	Incremental costs	Incremental QALYs	ICER
Adjusted base case	██████████	0.595	██████████
Baseline characteristics (age 51 starting age)	██████████	0.585	██████████
Full ITT including escalation	██████████	0.496	██████████
Full ITT excluding escalation	██████████	0.520	██████████
Moderate to severe including escalation	██████████	0.578	██████████
Exclusion of SSM and AdvSM	██████████	0.557	██████████
TKI subsequent treatment	██████████	0.595	██████████
Excluding stopping rule	██████████	0.827	██████████
Health state occupancy excluding crossover patients	██████████	0.595	██████████
Extended AE duration	██████████	0.595	██████████
QoL benefit for severe responders excluded	██████████	0.573	██████████
Avapritinib as treatment for AdvSM	██████████	0.595	██████████
Avapritinib and midostaurin as treatment for AdvSM	██████████	0.595	██████████
AE disutility for contusion, dry mouth, and photosensitivity (0.05)	██████████	0.595	██████████
AE disutility for oedema peropheral and periorbital oedema (0.16)	██████████	0.595	██████████

Abbreviation: AdvSM: advanced systemic mastocytosis; AE: adverse event; ITT: intention-to-treat; QALYs: Quality-adjusted life-year; SDT: Symptom-directed therapy; SSM: smouldering SM; PAS: Patient Access Scheme.

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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	██████
2. Name of organisation	The UK Mastocytosis Support Group (UK Masto)
3. Job title or position	██████, Board of Trustees
4a. Brief description of the organisation (including who funds it). How many members does it have?	The UK Mastocytosis Support Group (UK Masto) 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. We promote access to knowledgeable care and access to medications, and we 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.
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.	Blueprint Medicines paid for travel, room & board for two trustees of UK Masto to attend a gathering of leaders of mast cell disease charities for the purposes of strengthening our collective capacity through collaboration (February 2025). We were not told the amount spent, but travel was in coach. Avapritinib was not a topic of conversation. Blueprint Medicines paid for a breakfast for patient group leaders at the September 2025 meeting of the European Competence Network on Mastocytosis. We have not published any position on the technology or a comparator in the last 12 months. One of our trustees spoke about patient quality of life on an “industry” panel paid for by Blueprint Medicines at the annual meeting of the EAACI (June 2025) but did not speak about avapritinib and all views expressed were the trustee’s. UK Masto is part of a collaboration with a mast cell disease advocacy group in another country creating a registry to collect data about mast cell diseases. This project has been in development for many years and will involve multiple sites for input of clinical data as well as patient-entered data. Blueprint Medicines and Cogent Biosciences have given grants (\$200,000 and \$70,000 grants respectively made to the other charity in the collaboration in Summer 2025) to help support the development of the registry over the next several years. Funds are to be used to pay for the initial establishment of the platforms to be used for data collection and other associated costs. Thus far the money has not come directly to UK Masto, but we will benefit from this ongoing project, to which we are also making financial commitments with money raised from our community. The data will be owned by the charities, and a steering committee that is independent of the companies and includes patient representatives will oversee decision-making about what data are collected and who has access to the data for research.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	In Autumn 2025 we surveyed people with indolent systemic mastocytosis (ISM) and their carers in the charity's "private" Facebook group and people with ISM in an additional well-vetted and moderated international "private" Facebook group (where there are more people with avapritinib experience) about their experiences, symptoms, views on treatment, quality of life etc. This survey (n=53) included the full set of questions from the McQOL, a validated mastocytosis-specific QOL tool ¹ , along with additional questions specific to the NICE questions. In addition, we looked at data from the PRISM study ² (which our charity was involved in developing, analysing and writing up for publication) to give a broader view of the issues that arise for people with ISM.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?

ISM could use a name change because indolent implies that the condition does not have a significant effect on patient QOL. A person with moderate to severe ISM will have symptoms across multiple body systems that are unpredictable, potentially life-limiting, debilitating, frightening, painful, embarrassing, and socially limiting. Diagnosis and treatment are made more complex by the variability across patients in symptoms, triggers of symptoms, and response to existing medications.

Anaphylaxis In ISM anaphylaxis often occurs in response to unpredictable triggers. In our survey 64% of all patients had experienced anaphylaxis, higher than that reported in the research literature (Brockow³ reports 50%). The most common triggers of ISM anaphylaxis are insect stings, food, unidentified, drugs, and exercise; combinations of triggers that add in heat, aspirin and mechanical stimulation of skin lesions to the initial list are also common⁴. Anaphylaxis may present with cardiovascular collapse but no swelling or hiving, an uncommon presentation that means that patients and their carers often have to advocate to get emergency care.

- From a carer: "The NHS journey has been one long battle with professionals who have little to no knowledge of this condition or its symptoms. Particularly following episodes of anaphylaxis causing hospitalisation."
- "Biggest impact is when I have to have surgery as I've had 4 really bad reactions, one needing CPR. I'm about to have a hip replacement and although I have an anaesthetic protocol. I know that my children are really worried."
- A member had anaphylaxis the cold from opening the front door when her child went out to play in the snow.

Skin—itching, flushing, redness, swelling Most people with ISM have skin lesions on the trunk and thighs. When irritated they are raised and very itchy. In some people the lesions are so numerous they become confluent. People also get swelling and redness, and flushing red in response to a trigger. A common skin trigger is temperature extremes (too hot, too cold) or contrasts (inside from being out in the cold or jumping into cold water).

- "This condition first manifested as urticaria pigmentosa, the "rash" was quite substantial on his back and itched incessantly. This caused discomfort and embarrassment. The treatment was antihistamines and emollients. The antihistamines were only partially successful and the emollients ruined clothing and caused further discomfort with clothing sticking to the skin. This curtailed activities such as swimming and anything that involved changing clothes in shared spaces due to the discomfort of other people's reaction let alone the physical discomfort. The physical itching at times is intense. Not wanting to wear revealing items in summer to keep cool and wearing warm clothes in winter, exacerbates both physical and mental symptoms."
- "The [spots] which I was told would be confined to my torso are spreading down my limbs. It has deeply affected my relationships. I have always taken great pride in my appearance, and this has completely robbed me of my self-esteem."

Gastrointestinal—diarrhoea, epigastric pain, vomiting In ISM the infiltration of the intestines with clonal mast cells and/or the release of mast cell mediators from excess mast cells elsewhere in the body can lead to distinctive

episodes of sudden-onset diarrhoea with severe cramping. In 30+ years as a patient advocate I have heard numerous stories of people having these sudden humiliating experience of having the bowels release in public. In our queries about reasons ISM patients stop working, this symptom is often cited. Excess histamine release also leads to hyperacidity in the stomach which may not be fully managed by H2 blockers and/or PPIs at higher doses.

- “We take her meds bag with change of clothes and wipes every time we go outside the door. There has been many times when she has not made it to a loo in time. The worst time being by the River Thames on a sunny Sunday afternoon, miles from home and lots of people enjoying a walk by the river. She hid behind some trees and coped the best she could. We went to a nearby pub and she spent forty minutes in the Ladies having yet another Masto episode with cramps and diarrhoea. We do not venture very far these days as a result.”
- “We are fortunate to have two bathroom facilities in our home otherwise life would prove even more difficult as the symptoms worsen.”

McQOL categories of symptoms looking back at previous 2 weeks. Results from UK Masto survey of Autumn 2025.

Answer Choices	None	Somewhat	Moderately	Very	Very Much	Response Total
Itching	13.21% 7	32.08% 17	32.08% 17	11.32% 6	11.32% 6	53
Skin redness/swelling	16.98% 9	28.30% 15	22.64% 12	22.64% 12	9.43% 5	53
Sudden feeling of warmth and reddening of the face (flushes episodes)	22.64% 12	22.64% 12	22.64% 12	18.87% 10	13.21% 7	53
Diarrhoea/loose stools	22.64% 12	16.98% 9	32.08% 17	13.21% 7	15.09% 8	53
Fatigue/Exhaustion	5.66% 3	9.43% 5	26.42% 14	24.53% 13	33.96% 18	53
Headache	30.19% 16	16.98% 9	32.08% 17	16.98% 9	3.77% 2	53
Muscle or joint pain	7.55% 4	11.32% 6	33.96% 18	22.64% 12	24.53% 13	53
Difficulty concentrating	5.66% 3	24.53% 13	28.30% 15	18.87% 10	22.64% 12	53

Fatigue is common and is exacerbated by use of antihistamines and by poor sleep.

- “Let me daughter down badly due to being exhausted after work. Would fall asleep around 6pm.”
- “My kids have suffered the most and my ex, who is still in my life to help me. I'm just not the energetic person I was. I am sick and fatigued daily. I try my best to not let it affect anyone, but it does.”

Pain and Osteoporosis Pain in the long bones is common, as are joint and muscle pain, headache and pain from mastocytosis-induced osteoporosis. Management is made difficult by the likelihood that NSAIDs and opiates may not be tolerated.

- “If there is something that I miss [it] is golf and fishing because I have osteoporosis through ISM.”

	Cognitive Effects ISM commonly causes neurocognitive symptoms including trouble with memory, word finding, and cognitive acuity.⁵ Patients can find it challenging adjusting to losing these functions, and carers say the same. The symptoms can be transient (worse when exposed to a trigger) so they can be difficult to measure, and function can be difficult to predict for a given time, with consequences for employment. • “I don’t know from one moment to the next whether I’m going to be set off by something I breathe in (fragrances, cleaning products) or something I eat. I try not to plan important meetings for after lunch just in case and I wear a mask on public transport because everyone is covered with scents in the morning. It makes me really anxious (another trigger) not to know if I’m going to have access to my brain when I need it. It has prevented me from seeking challenging work and generally affects my confidence. • “On a bad day, he is aware that driving is not wise... I attend all my husband’s appointments with him so that I am aware of what is being discussed. There are days when we converse normally and another day when he has completely forgotten what was discussed.” Social/Emotional ISM patients often talk about the unpredictability of flares, the diversity of symptom triggers, the challenges of always needing to advocate for oneself, and the disease itself (depression, irritability, anxiety) as reasons they feel alone and down. • “It has affected relationships and socially because of the unpredictability of trigger episodes. I’ve had to cancel plans last minute. There is an aloneness with the disease because so few understand it.” • “Mostly for me it has changed my eating and drinking habits. I hate having to tell people the main things I cannot eat and react to. [It is] stressful going out for a meal especially to someone’s house - I am often ill after a meal out... I makes me feel people think I am making a fuss... My Masto affected my relationship with my mother as until I had a [bone marrow biopsy] she never took my situation seriously. The disease is constantly in the background of my life. What can I eat? Will I have diarrhoea or be sick. I always carry cetirizine with me in case I feel nauseous when I am out.” • “Family and work don’t know what to make of it and just think it’s an allergy. Difficult for people to understand as no one has heard of it.” • “A carer says: One evening, early in our experiences of anaphylaxis he collapsed and when the responder arrived his heart had stopped. I have not forgotten that experience and it haunts me.” • “I am completely unable to eat or drink what I used to. In fact, I can no longer live as I used to. It has completely robbed me of the pleasures of life that my wife and I had looked forward to on our retirement. I rarely sleep through the night. I can no longer exercise or socialise confidently. I feel like a leper, marked and isolated. It has got to the point that I feel I exist rather than live.”

Triggers and their Avoidance

The avoidance of triggers is both a strategy for improving QOL—fewer reactions if not exposed— but it is also a burden that can be severely limiting to social and professional life. In the PRISM study, the most commonly reported triggers were foods, temperature changes, emotional stress, medication, and airborne products. Patients need to be aware of the increased risk of anaphylaxis from anaesthesia, pain medications and certain other medications, meaning they/carers must advocate for their safety during any medical interaction.

- “My days now revolve around managing symptoms and evaluating risk.”
- “I’m now allergic to some foods and I cannot drink alcohol, [react] to temperature changes so I find it difficult to leave the house without having a reaction (hives, itching, stomach cramps, diarrhoea) so I don’t socialise as much, my triggers change a lot too from day to day so I have to be careful and carry epipens.”
- “Alcohol, intense exercise, spicy foods, showers / bath make symptoms worse (flushing, stabbing feeling in skin).
- “I avoid going shopping and into crowded places due to the perfumes, smells, air freshener and people vaping. Now its winter I avoid going outside as much as possible as cold is a major trigger for me. I am currently unable to exercise as this sends me into a flare.”
- “My day to day is work and home, when home I sleep a lot due to fatigue, or disturbed nights due to blood pressure dropping causing chills, or skin flares and bone pain. My youngest children are now my carers; they monitor me all the time...get my meds or tell me when we are out that it smells strongly of perfume. My children assist me doing shopping and they go down the aisles that have soaps. They often have to cook for themselves as I am too fatigued or sore to do it. Due to pain and not being able to use most cleaning products, I have hired a cleaner who attends the house once a week when I am not home. On leaving she has to leave all the windows open to allow any scents to dissipate. As time moves on, I am becoming more isolated from family and friends. My youngest child gets support via young carers, for myself the only support I get is via Mastocytosis UK.”

Employment In the UK portion of the PRISM study (n=50 UK ISM patients) half said ISM affected their employment, 32% reduced their hours, 16% voluntarily quite their job, 8% took early retirement, 18% had gone on medical disability and 6% had been terminated in their job (multiple answers were permitted).

“DWP has declared me unfit for work, potentially for life. I had to leave 2 jobs, my partner left her job to work from home so she can support me.” “I am currently on disability because I have difficulty maintaining my previous employment.” “I had already retired on health grounds when I was diagnosed with urticaria pigmentosa.” “It was in my best interests that I changed my job being a dairyman with 18 days on and 3 days off to a job with more time off. Suffered fatigue and had no energy for anything.” “I am self-employed so have the ability to make my own schedule which is helpful.” “I have to take a lot of time off work, and it affects my role as I am a "key dependant" individual in the company.” “I work full time and it takes most of my energy- weekends are for recouping and sleeping.”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	In our survey the non-avapritinib patients (n=44) were nearly all on an H1 antihistamine, 56% were on an H2 blocker, 43% on a PPI, 38% on Nalcrom, 25% on montelukast, 31% on bisphosphonates, with 1 patient on omalizumab, and 2 on oral corticosteroids. This polypharmacy is common, as also reported in the PRISM study⁶. Medications help: “It helps decrease the amount of flare ups I have” “I take fexofenadine and I’m sure it’s made a difference”, “I think cetirizine helps? Gives dry mouth”, “Ketotifen was life changing at the time when I was so ill. The disadvantage is that I have to take so many different H1 and H2 each day just to keep functioning at a reasonable level.” “[They] don’t stop the symptoms fully, they do lessen the severity... they improve enough for me to at least function.” “After many years of poor sleep, taking antihistamines stopped the 2am wake ups and I sleep well. My asthma has improved and I am no longer requiring frequent prednisone.” Other patients are less sure: “You live in hope that they help. You have no idea of their capability or if you would be the same without them.” Medications are inconvenient and cause side effects: “There are too many tablets to take, each medication deals with one separate symptom of ISM, many of the medications have serious side effects and some can cause drowsiness. Some have to be taken 4 times a day, 3 hours before food—that takes planning and stops spontaneous outings. I feel as if the meds are ruling me!” “High doses of antihistamines affect my eyes.” Allergic to medication: “I have had allergic reactions to fexofenadine, due to being given a different brand, so I don’t take these anymore as chemist can’t give me the same brand every time!!” Medications haven’t helped: “None of my medications have helped with my symptoms yet. I’m waiting for a medication that will help me.” Patients also mentioned problems with stock of medicines (this is most often ketotifen and sodium cromoglicate). Medications leave some symptoms untouched: We used a slider scale in our survey to ask “How well do you feel your current medications control your symptoms”. The average was 44% (SD 26) for non-avapritinib folks. We also asked which symptoms are not well-controlled on the current treatment. The most common uncontrolled symptoms were fatigue, skin symptoms, bone pain, lower GI, upper GI, cognitive symptoms, and bone, muscle and joint pain.

8. Is there an unmet need for patients with this condition?	There is a significant unmet need for people with moderate to severe ISM. In our survey we asked patients what symptoms they had while taking their current treatment. Even while taking the best existing options, the non-avapritinib patients (n=44) reported the following: trouble remembering (84%), fatigue (84%), itching/hiving/flushing (82%), difficulty concentrating (80%), trouble with word finding (75%), lower GI symptoms (75%), bone pain (73%), low mood (68%), headache (57%), dizziness and fainting (57%), upper GI symptoms (48%), vomiting (16%). In addition, patients are dealing with anaphylaxis (24% reported having anaphylaxis more than 6 times), osteoporosis (men and women of all ages), as well as the risk that their mastocytosis might progress to an advanced form. The existing treatments (BSC) either modify the way some of the mediators released by mast cells affect the body, or are marginally effective at stopping the release of mediators. There are more than 100 mediators that mast cells can release, and we ineffectively target three: histamine, leukotrienes and occasionally prostaglandins. Sodium cromoglicate and ketotifen aren't very effective mast cell stabilisers. And omalizumab is appropriate for a small number of people (and sometimes induces anaphylaxis). This approach, which involves polypharmacy with each medicine often coming with side effects, is burdensome to take and just doesn't work very well for people with moderate to severe ISM. What people with ISM need are medications that go to the core of the problem—by addressing the clonal/proliferative element so that there is a normal number of (unmutated) mast cells in the body, and/or by decreasing the mast cell's sensitivity to triggers.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	<i>Overall improvements in a range of domains</i> • “Every single moment of the day was affected [before taking avapritinib]. Sleeping (waking in the night with itching and anaphylaxis if hot), washing (could not have baths and no long hot showers, so if washing hair had to be cool shower), general daily tasks had to be done in small doses, hoovering, cooking by hot hob) and many other daily tasks. Could not do any exercise. Caution with what to wear on cold days if then walking into shops with heating. Permanent umbrella in the sun to try and stay cool. Children had to learn how to cool car down, so I did not get into a hot car. Taking care not to put myself into situations where I might get embarrassed/flushed as would cause anaphylaxis. Same with any situation where someone may get excited. The list could go on and on. But not one single attack since being on treatment.” • “After about 6 weeks on the medicine I noticed lessening of symptoms.” • “For me the advantage of taking Avapritinib has been that my skin doesn’t itch constantly, that my skin reactions are so much milder, & I have noticed less foggy brain.” • “I have noticed a significant improvement in my symptoms. My tryptase dropped from 59 to 18 within a month. Bone pain and skin lesions/spots are gone. Overall, I feel much better and have my energy back.” • “It has been unbelievable for me...a little like magic! To think this tiny little pill could help with all the varied symptoms I was experiencing for so many years. I’m thankful that I have a wonderful doctor who thought outside the box to diagnose me and then to work with me until we found the best treatment.” • “For me the advantages are: Almost complete disappearance of the rash and the discomfort, sore skin, itching and flushing that went with it. Reactions are much rarer and milder. No diarrhoea or vomiting. No anaphylaxis so no hospital admissions. Reduced fatigue. I can manage a small alcoholic drink, though I still flush a little. Increased stamina. Friends are so very frequently telling me how much more well I look. • “I went on avapritinib (Ayvakit) to stop anaphylaxis. It has stopped anaphylaxis, my spots have faded, my breathing has steadied, I’m not tired all the time.” • Bone pain is decreased, energy is better and the fear of enjoying life is gone. I can go places alone and travel and not be fearful that doctors can’t help me or that I might die from anaphylaxis. I can shower without breaking out in hives every day.” • “Return to my normal life.” • “100% life changing. I can do everything you would expect to be able to do as a normal person, including exercise, with absolutely no symptoms.” • “I never realized how much it was affecting my mood, focus, and motivation until I started taking avyakit and after about 6 weeks it was if a fog lifted and it only continues to improve (all symptoms) as my treatment continues (I’m on

Patient organisation submission

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

	my 4 month). Other meds helped some but this was a game changer. I have hope again that the disease will not steal my well being.” Anaphylaxis We asked avapritinib users about the frequency of anaphylaxis since starting the drug: 2/9 had never had anaphylaxis, 6 said they’d had it less often since avapritinib, 0 said they had it about the same frequency, and 1 said they had it more often (this last patient is a bit confusing they have been higher dose of avapritinib (200 mg), so the situation is a bit unclear.) “My anaphylaxis had been related to heat and exercise. Since beginning Avapritinib, I have not experienced anaphylaxis to date although I exercise regularly.” “Since very soon after starting Avapritinib I have had no anaphylaxis and only a very small number of very mild reactions, just mild cramping and a little itching. This has all become even rarer as time passes.” Decrease in BSC medications We asked those taking avapritinib if they had been able to decrease their use of “best supportive care” medications (BSC). Of the nine patients, one was instructed not to decrease meds, one was given permission but hadn’t yet started to, one had not decreased meds, and six had decreased their BSC medications.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We heard from nine people who had taken avapritinib in our survey and their comments were consistent with what we have heard in patient forums over the past several years as more patients have used avapritinib and what we have seen in published research. Some patients report no side effects, where others report side effects that are ongoing, transient, or resolve with discontinuation: oedema around the eyes (ongoing or resolving in time), lightening of skin, fatigue, decreased platelet count, hair thinning. Patients told us: “In the beginning there were side effects, but these have greatly lessened.” “None. I have had no adverse symptoms at all.” “Puffy eyes every day. I am very fair skinned anyway, but my skin has become paler and translucent.” “None considering the alternative.” “Platelets dropped from 290 to 80 in three months. Blood work this week will determine if I’ll have to reduce current prescription of .25mg per day.” “My hair has thinned. I have had gastrointestinal effects, but those seem to be lessening as I adjust to the medicine.” “The main downside for this med has been increased fatigue that often require daily naps to get through the day.” “No disadvantage.”

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.	At present it seems clear from observing in patient forums in countries where avapritinib is already on the market that there are patients who are having a radical improvement in their quality of life on avapritinib and are without side effects. And there are others for whom the improvements are tempered by some side effects (that are still tolerated and are judged by the patient to be better than the symptoms of ISM or they would stop the medication). This is also evident in our small sample in our survey. It is not clear to me from the research or from interacting with patients what distinguishes the completely transformed patient from the one who is happy to have avapritinib but it is not fully transformed. Moderate to severe patients will vary in what their worst symptom is, but the data from the trials suggest that improvement can occur in any domain.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The key equality issue in ISM is the variability in access to knowledgeable care. This affects speed of diagnosis, accuracy of diagnosis, optimisation of existing treatments (which can take quite a bit of trial and error), advice about trigger avoidance, and attention to symptoms not normally managed under the doctor's specialty (e.g. GI for a dermatologist, osteoporosis for an allergist, etc.) At present there are two recognised centres of excellence in the UK, with a handful of additional centres with experienced doctors and larger patient pools. Information will be the limiting factor in use of avapritinib, and a more complex set of procedures regarding how and on whom the medication can be used will make it more likely that patients with less experienced doctors will have less access.

Other issues

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• People with moderate to severe ISM have poor quality of life. The PRISM study found that EQ5-D scores were lower in ISM than in lung cancer and rheumatoid arthritis patients, and our survey has illustrated the poor quality of life. • Existing medication manages some but not all of ISM symptoms, often causes side effects, can be burdensome to take and does not change the trajectory of the disease. People with moderate to severe ISM need medications that address the underlying problem—mast cell over-proliferation and excessive sensitivity to triggers. • People with moderate to severe ISM are diverse in their presentation of symptoms and in their tolerance of particular medications. No single medication has yet suited all of them. It is reasonable to assume that there will be some patients for whom avapritinib will be lifechanging (based on what patients who've taken it have told us) and others who may choose not to take it. • There are three additional areas where patients are hopeful about the effects of avapritinib, though they were difficult to capture in the trials because of the maths of rare disease trials and of infrequent events—frequency of anaphylaxis, likelihood of osteopenia/osteoporosis, and effects on progression of ISM to advanced SM. (Early signs seem auspicious). • People with ISM need access to more effective to participate fully in society including employment, family life and social life.

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

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¹ Siebenhaar F, et al. Development and validation of the mastocytosis quality of life questionnaire: MC-QoL. Allergy. 2016 Jun;71(6):869-77

² Triggiani, M. et al. (2025), Patient-Reported Outcomes and Provider Perceptions of Systemic Mastocytosis: Results From the PRISM Study. Clin Exp Allergy, 55: 784-794

³ Brockow K et al. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008 Feb;63(2):226-32

³Ibid

³ Sophie Georgin-Lavialle, et al Mastocytosis in adulthood and neuropsychiatric disorders, *Translational Research*, Volume 174, 2016, Pages 77-85.

Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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.

About you

1. Your name	[REDACTED]
2. Name of organisation	British Association of Dermatologists (the BAD)
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health and Social Care, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
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.)	Cutaneous mastocytosis is a difficult-to-manage, chronic condition which, when established, affects adult patients for the rest of their lives but often resolves in children. Patients can have very visible skin changes (TMEP) which can impact on their mental health and limit the physical activities that they choose to participate in, as their skin can be very itchy with swelling and flushing. This can be made worse by changes in skin temperature (e.g. running in the cold), by certain foods, and by medications including general anaesthesia. Furthermore, these patients are at higher risk of osteoporosis and its associated morbidity, and anaphylaxis when they have systemic involvement. The main aim of treatment is to improve the management of symptoms associated with indolent mastocytosis, including skin presentations, to allow patients to live as normally as possible.
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.)	For cutaneous symptoms, we would expect patient-reported outcomes of itch, skin flushing in response to temperature changes, etc., and swelling to reduce significantly (by at least 50%) with a DLQI reduction of at least 50%. We would also expect patients to see a reduction in other symptoms including headaches, fatigue, irritability and brain fog, as well as gastrointestinal side effects and bone pain.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for novel and effective targeted treatments for adult indolent systemic mastocytosis (ISM) with and without cutaneous involvement, given that the current standard of care offers limited effectiveness and does not address the appearance of skin symptoms, which often cause unrecognised – yet detrimental to the patient – psychological distress. Avapritinib offers an opportunity to manage symptoms of mastocytosis effectively often presenting initially to dermatologists with skin lesions.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current best supportive care includes H ₁ and H ₂ -antihistamines, montelukast, sodium cromoglycate, proton pump inhibitors, vitamin D and calcium supplements (for associated osteopenia) adrenaline autoinjectors, narrowband-UVB, PUVA and the occasional off-label use of omalizumab for uncontrolled anaphylaxis.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no published consensus UK guidelines for ISM in dermatology. However, there is guidance in use, including that by the Primary Care Dermatology Society and international guidelines on systemic mastocytosis for comprehensive diagnosis and management e.g. J Natl Compr Canc Netw. 2024 Jun;22(2 D):e240030.
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.)	There is consensus amongst dermatologists about management of mastocytosis in adults, which is best supportive care, including the treatments outlined above. Consensus is that patients have an annual tryptase, blood count and liver profile, yearly complete skin and abdominal examination for organomegaly, and 3- to 5-yearly DEXA scan. Patients are counselled about the risk of anaphylaxis (up to 50% of adults with ISM) and recommended to carry at least one adrenaline autoinjector in specialist centres.
9c. What impact would the technology have on the current pathway of care?	It would offer an additional treatment option for patients with moderate-to-severe symptoms not controlled with conventional treatments – these include H ₁ and H ₂ -antihistamines, montelukast, sodium cromoglycate, proton pump inhibitors, vitamin D and calcium supplements (for associated bone density loss) adrenaline autoinjectors, narrowband-UVB, PUVA and the occasional off-label use of omalizumab for uncontrolled anaphylaxis. At present, we do not have anything else to offer these patients, resulting in significant morbidity and an unmet need.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Existing supportive treatment will be used for all patients initially, however, if symptoms cannot be controlled with this and patients have moderate-to-severe symptoms, then this technology will provide a new, additional option.
10a. How does healthcare resource use differ	At present, we do not have any targeted treatment for ISM, and avapritinib would be the first specific, targeted therapy directly inhibiting D816V-mutated KIT.

between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be used in secondary care, by clinicians with experience of mastocytosis. Few specialist clinics exist because of the rarity of the disease; therefore, we would recommend that this is managed in secondary care by doctors with experience in managing this condition.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Avapritinib is already prescribed in adult patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated haematological neoplasm, or Mast cell leukaemia, as well as for patients with unresectable/metastatic gastrointestinal stromal tumours. Therefore, there is already experience of prescribing the drug and additional facilities/equipment are not required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Cutaneous lesions associated with mastocytosis can have a highly negative impact on a person's self-confidence and lifestyle opportunities - this is especially true for patients with extensive skin involvement. Therefore, managing skin lesions with effective treatment can have a meaningful impact on patients' lives, enabling them to become more involved and better-functioning members of society.
11a. Do you expect the technology to increase length of life more than current care?	The technology is primarily to improve quality of life rather than extend length of life.
11b. Do you expect the technology to increase health-related quality of life more than current care?	ISM can lead to significant systemic complications. These include debilitating effects on bone health such as osteopenia and osteoporosis, neurocognitive impairments, recurrent allergic reactions including life-threatening anaphylaxis, and a risk of progression to smouldering or advanced systemic mastocytosis. These manifestations often remain under-recognised and inadequately managed with current treatment options. Avapritinib offers a targeted therapeutic approach, directly inhibiting the common D816V KIT variant and has the potential to alleviate a broad spectrum of symptoms beyond cutaneous involvement. Its use represents a meaningful advancement in the management of ISM with and without cutaneous involvement, with the potential to improve physical functioning, reduce disease burden, and enhance overall quality of life for affected individuals.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is expected that patients with more severe symptoms would benefit the most, however, all adult patients with symptoms could potentially benefit more than the general population.

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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Avapritinib is a daily oral tablet and is therefore not more difficult for patients to take than their current oral antihistamines. https://ayvakit.com/wp-content/uploads/AYVAKIT AdvSM Dosing and Management Guide.pdf Patient monitoring MONITOR YOUR PATIENTS' PLATELET COUNTS¹ Platelet monitoring should be performed prior to initiating therapy and throughout therapy as shown in the schedule below.¹ <table><tr><th>Time on therapy</th><th>Monitoring plan</th><th>Treatment plan</th></tr><tr><td>Prior to initiation</td><td>Perform platelet count.</td><td>AYVAKIT is not recommended in Advanced SM patients with platelet counts <50 x 10⁹/L.</td></tr><tr><td>First 8 weeks</td><td>Perform platelet count every 2 weeks regardless of baseline platelet count.</td><td rowspan="2">If platelet count <50 x 10⁹/L occurs, interrupt AYVAKIT until platelet count is ≥50 x 10⁹/L, then resume at reduced dose. If platelet counts do not recover above 50 x 10⁹/L, consider platelet support.</td></tr><tr><td>After 8 weeks</td><td>Monitor platelet counts: • Every 2 weeks if values are <75 x 10⁹/L (or more frequently as clinically indicated) • Every 4 weeks if values are 75-100 x 10⁹/L • As clinically indicated if values are >100 x 10⁹/L </td></tr></table>	Time on therapy	Monitoring plan	Treatment plan	Prior to initiation	Perform platelet count.	AYVAKIT is not recommended in Advanced SM patients with platelet counts <50 x 10 ⁹ /L.	First 8 weeks	Perform platelet count every 2 weeks regardless of baseline platelet count.	If platelet count <50 x 10 ⁹ /L occurs, interrupt AYVAKIT until platelet count is ≥50 x 10 ⁹ /L, then resume at reduced dose. If platelet counts do not recover above 50 x 10 ⁹ /L, consider platelet support.	After 8 weeks	Monitor platelet counts: • Every 2 weeks if values are <75 x 10⁹/L (or more frequently as clinically indicated) • Every 4 weeks if values are 75-100 x 10⁹/L • As clinically indicated if values are >100 x 10⁹/L
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14. Will any rules (informal or formal) be used to start or stop treatment with the	Patients who fail to respond to best supportive care and have moderate-to-severe symptoms of ISM would be considered to start treatment. In the PIONEER study, 24 weeks was used as an endpoint to assess response to											

technology? Do these include any additional testing?	treatment response, with the primary endpoint measurement of reduction in total symptoms score. The study recorded improvement of at least 30% and 50% of total symptoms score at week 24. It is expected that this will form the basis for the rules to stop treatment.
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?	Not that we are aware of.
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, avapritinib directly targets the mutated tyrosine kinase that drives this condition. At present, treatment is nonspecific and aimed at broadly keeping symptoms under control, and as a result, has limited efficacy.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. In patients with advanced systemic mastocytosis, avapritinib has been demonstrated to have disease-modifying effects, including reduction in the mast cell burden and normalisation of organ damage. It is therefore expected that it would significantly impact the quality of life in patients with ISM, for which the only current treatment options are best supportive care.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. At present, there is no specific, targeted, treatment for this population group, and avapritinib would change that, as it directly targets KIT D816V-mutated tyrosine kinase that drives nearly all adults with mastocytosis.
17. How do any side effects or adverse effects of the technology affect the	In part 3 of the PIONEER trial, only 5 patients out of 235 were discontinued from the study because of an adverse effect, so it is anticipated that significant side effects would be low. Dose reductions would be possible for patients

management of the condition and the patient's quality of life?	if needed, and guidelines already exist for patients having avapritinib for other conditions such as advanced systemic mastocytosis.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	
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?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were 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?	

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	None that we are aware of.
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that we are aware of.
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The first targeted therapy for ISM – a difficult-to-manage, chronic condition which affects patients for the rest of their lives when established – directly inhibiting the common D816VKIT variant present in the majority of adults with cutaneous and systemic mastocytosis • Represents a step-change in managing ISM, as current management approach involves best supportive care. • Potential to improve patients' quality of life significantly. • •

Thank you for your time.

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	██████████
2. Name of organisation	British Society of Haematology
3. Job title or position	Haematology Consultant
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society of Haematology promotes excellence in the study, research and practice of haematology for the benefit of professionals and the wider public.
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.	Not that I am aware of.
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.)	ISM is the most common subtype of systemic mastocytosis (SM) which is a clonal haematological neoplasm driven in the majority of patients (> 95%) by the <i>KIT</i> D816V. Patients with ISM can often experience longterm multiple symptoms that can have a significant and negative impact on their ability to function, carry out activities of daily living or need adjustments made at home / work to enable them to function leading to a poor quality of life. Symptoms are systemic and unique to patients and can effect their skin (80% have a rash or variable clinical cosmetic impact and itching/ flushing or can urticate depending on triggers which lead to release of mediators – pro- inflammatory- from mast cells). Symptoms can affect the GI tract leading to nausea, vomiting, abdominal pain, bloating and diarrhoea and or constipation, allergic type reactions affecting the respiratory systems – upper respiratory tract, musculoskeletal and also neurocognitive effects as these mediators cross the blood brain barrier – leading to difficulty in focus/ concentration, memory problems, inability to carry out instructions, calculations and word recognition – impairing functional ability at work and at home and impacting quality of life. Some patients present with and suffer from anaphylactic reactions and these can be life threatening in their own right especially if no trigger is identified. Avapritinib is an oral, highly selective and potent inhibitor of D816V mutated <i>KIT</i> so targets the mutation that drives this disease. The main aim of the treatment is to improve symptoms and QOL and prevent progression or further disability due to mast cell mediator release. This is based on the outcome of the PIONEER trial: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200339 J Gotlib et al. Avapritinib vs Placebo in Indolent Systemic Mastocytosis. 23rd May 2023/ NEJM Evid 2023 ;2(6). The PIONEER trial (NCT03731260: part 1/2/3) to assess the efficacy and safety of avapritinib 25mg once daily (potent direct C-KIT inhibitor) in adult indolent systemic mastocytosis patients with moderate to severe symptoms, on at least 2 anti-mast cell mediator optimised therapies with persistent symptoms demonstrated a significant improvement with decrease in overall symptom burden and improvement in quality of life for those patients on avapritinib vs best available supportive care. Randomisation was 2:1 (avapritinib vs placebo both with best supportive care). Total number of patients enrolled 212 (141 on avapritinib and 71 placebo arm). TSS scores $\geq$ 28 (range 0-110) based on ISM-SAF©. Primary end point was mean change in TSS based on a 14 day average of patient reported severity of 11 symptoms. Secondary end points : reductions in serum tryptase, blood <i>KIT</i> D816V variant allele fraction (VAF $\geq$ 50% and $\geq$ 30%), reduction in bone marrow mast cells ($\geq$ 50%) -all 3 reflecting any changes in mast cell disease burden and quality of life measures. Results from baseline to week 24 showed: Median duration of treatment part 2 was 5.6 months (24.1 weeks) for both groups – 96% avapritinib pts and 93% on placebo continued on part 3 open label extension to receive 25mg avapritinib. • TSS scores decreased by 15.6 points in avapritinib treated patients (95% CI -18.6 to -12.6) vs 9.2 points in the placebo cohort (95% CI- -13.1 to -5.2); P < 0.003. • 76/141 patients on the avapritinib arm had a 54% (45%-62%) reduction in serum tryptase compared to placebo 0/71(0%) achieved $\geq$ reduction. • Avapritinib was generally well tolerated with commonest side effects reported being oedema, increases in ALP – transient, mostly grade 2 and manageable. Very few treatment discontinuations due to adverse events.

	• Mean (SD) change in the most severe symptom reported by patients was -2.2 on avapritinib arm vs -1.4 in the placebo arm. • 80/118 (68%) avapritinib arm patients had $\geq 50\%$ decrease in <i>KIT</i> D816V VAF vs 4/63 (16%) in the placebo arm. $P < 0.001$ • 56/106 (53%) had a $\geq$ reduction in bone marrow mast cell burden vs 13/57 (23%) in the placebo arm. $P < 0.001$. • BSC usage was reduced / discontinued in 24% of the avapritinib arm of patients vs 13% in placebo cohort by week 24. • BSC increase use was noted in 11% of patients on placebo vs 8% avapritinib arm. • QOL improvements were noted avapritinib vs placebo over 24 weeks as measured by ;SF-12 physical scores increased by 20% vs 12% ;SF-12 mental health scores increased by 12% vs 6% ;EQ-VAS scores increased by 19% vs 5%; MC-QoL scores decreased by 34% vs 18% After the 24 week crossover in the open label part 3 (26 pts) completed an additional 24 weeks and there was a mean TSS improvement in those who were on the placebo.

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.)	ISM patients has symptoms that impact on their quality of life as a result of the clonal mast cells releasing mediators which can have local effects on the organs infiltrated or distant/ systemic affects as a result. The mast cell disease is variable and can be low in some patients who can still suffer from significant symptoms depending on their individual triggers. Patients with ISM do not have any end organ damage typically resulting in organomegaly – enlarged liver/ spleen size or any abnormal blood counts so these cannot be used to measure any clinical responses unlike patients with advanced systemic mastocytosis. As we are assessing symptom burden and improvement this should be the clinical response measured to confirm benefit of treatment with avapritinib. Decrease in symptom burden and severity, improvement in overall quality of life as a result, decrease in those patients who suffer from anaphylactic reactions as easily documented but this accounts for a small proportion of ISM patients, decrease in use of best supportive / additional anti mediator treatments needed / used over time. Other measures which are important and take into peripheral but not usually measured outcomes formally would be ability to ability to perform tasks which we not possible at baseline – increase working hours, ability to spend more time with family/ socialise/be less dependent on carers or support from family to manage activities of daily living. The PIONEER trial demonstrated that using a 2 week daily average of the ISM-SAF form improvements in the TSS scores for patients of avapritinib 25mg od vs those in the placebo arm and across all 11 domains over 24 weeks. This improvement was also shown in the additional QOL assessments forms – MCQoL, EQ-VAS, SF-12 physical and mental health scores. Currently there is no standardised form utilised uniformly in clinical practice as patients will present to different disciplines and there can be different QOL/ PROs available. A trend in improvement over time of symptoms, QOL, reduction in supportive medications would be an important clinical significant outcome rather than a fixed – pre-determined percentage.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes -there is an unmet need for patients who suffer with extremely symptomatic ISM and have unpredictable reactions to mast cell mediator release despite optimisation of the currently available best supportive combination of anti-mast cell mediator treatments. Patients can have a debilitating responses/ triggers or unknown triggers leading to inability to function, have an extremely poor quality of life and require care or support to manage. This targeted KIT D816V inhibitor directly targets the clonal mast cells, leading to decrease in the mast cell mediator release and mast cell disease burden; reduced tryptase, reduced visible skin lesions, reduced bone marrow mast cell numbers and quantifiable mutation levels (VAF) and hence not only has an impact in reducing symptom burden but potential longterm disease modifying effects. For patients on the PIONEER trial avapritinib has made a significant improvement above and over standard therapies. Patient -Reported Outcomes and Provider Perceptions of Systemic Mastocytosis: Results From the PRISM Study. Massimo Triggiani et al. Clinical & Experimental Allergy, 2025; 55:784794; https://doi.org/10.1111/cea.70101784 Methods: PRISM (funded by Blueprint Medicines Corporation) was composed of two independent surveys: a 119-item patient survey on diagnosis, symptom burden, quality of life (QoL) and work impact; and a 103-item healthcare provider (HCP) survey on approaches to SM diagnosis and management. Results: Data were evaluated from 540 patient respondents from Italy (n = 136), France (n = 112), the UK (n = 101), Germany (n = 83), Spain (n = 64), Austria (n = 26) and Switzerland (n = 18). 237 pts had ISM and 50 were UK patients. Patients reported a high symptom burden and reduced physical functioning and mental health due to SM, despite taking, on average 5-6 medications. 38% reported experiencing anaphylactic episodes within the previous year. With 21% having 5 or more episodes of anaphylaxis. 43% of ISM patients reported that SM impacted their ability to work, 24% needing to reduce hours and 17% needing to stop work completely. Yes – an unmet need for healthcare professionals who manage these rare patients in their specialties/ with multidisciplinary input and support as best as they can and access for the symptomatic patients to avapritinib with education on the side effect profile although generally well tolerated and managing these patients over the longterm.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current treatment options are all supportive and symptom management based to deal with the fallout of mast cell mediator release. Avoidance of triggers if identified – some food products, medications, environmental triggers (temperature changes). Then the mainstay is anti-mast cell mediator medications in variable combinations depending on response. These include anti histamines (anti H1 and anti H2 receptor antagonists – short and long acting: Loratadine, Cetrizine, Piriton, Fexofenadine, Ketotifen, Nizatidine, Cimetidine or Famotidine), mast cell stabiliser – Sodium chromoglycate. These medications are often needed in higher doses than recommended in the BNF for ISM patients. Tricyclic anti-depressants for low mood, pain management – Amitriptyline, Gabapentin. Patients who have anaphylaxis associated with wasp stings maybe treated with wasp venom immunotherapy which is recommended as longterm treatment in patients with a confirmed diagnosis of ISM currently. These patients with anaphylaxis will auto inject with adrenalin pens to manage their anaphylactic episodes and some may need corticosteroids post episode if severe or more than 1 adrenalin injection. Omalizumab – anti IgE maybe available for patients with chronic urticaria associated with their ISM. PUVA treatment may be available for patients with a significant rash – skin involvement of their mast cells which is cosmetically disturbing and/or leading to itching/ flushing. The impact cosmetically on skin lesions is transient whilst being treated. For severe reactions, corticosteroids maybe required for short term in some patients and low dose in some patients to control or reduce flares in some patients. To manage the 30% risk of osteopenia / osteoporosis supplementation with Vitamin D/ Calcium or treatment with bisphosphonates is required. For very severely affected patients who have been refractory to multiple anti mast cell mediator therapies – some form of cytoreductive treatment (off label use) maybe considered: Cladribine/Interferon alpha/ hydroxycarbamide. Clinical trials are recently available for patients if they can take part.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No current UK clinical guidelines available and are being worked on in the next year. Valent P et al. Personalized Management Strategies in Mast Cell Disorders: EACMI-AM User's Guide for Daily Clinical Practice. J Allergy Clin Immunol Pract. 2022 Aug;10(8):1999-2012.e6. doi: 10.1016/j.jaip.2022.03.007. Epub 2022 Mar 25. PMID: 35342031. USA NCCN guidelines are available as a guide: Systemic Mastocytosis, Version 3.2024JNCCN.org Volume 22 Issue 2D June 2024
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the	No well-defined care pathway currently and clinicians who manage ISM patients vary – dermatologists, haematologists, immunology / allergists depending on symptoms patients present with clinicians with an interest. There is no standardised consensus or UK guidance on managing these patients and as they are rare – clinical experience is variable and speciality specific.

NHS? (Please state if your experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	Majority of patients with ISM that are symptomatic are under the care of haematologists/ dermatologists and some allergists/immunologists. There is no UK defined pathway of care but historically patients who are treated with TKIs have usually been under the care of haematologists as there is experience with managing these targeted drugs. I would anticipate more centres will have a multi-disciplinary approach to diagnose and manage these patients in a secondary care setting and this is evolving.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently avapritinib is not available / or in use in routine NHS clinical practice.
10a. How does healthcare resource use differ between the technology and current care?	There will need to be introduction into clinical practice / pharmacy of the technology and education of clinicians and patients. There will be anticipated increase in OPA reviews of patients who start avapritinib initially and then once established 4-6 monthly reviews. These symptomatic patients are likely to be seen more frequently than those who are minimally symptomatic and in annual reviews so should not be a significant increase in OP activity longterm.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Technology should be used in secondary care setting and specialist clinics – currently most SM patients are seen by haematologists with an interest in myeloproliferative neoplasms.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment to introduce technology will mainly be a focus on education and training to recognise symptom management and potential side effects. No additional facilities/ equipment is necessary.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – as already discussed in section 6 with the results of the PIONEER trial and outcomes.
11a. Do you expect the technology to increase	Life expectancy for ISM patients is ‘normal’ compared with an aged-matched population and so there is not an anticipated further increase in length of life but more significantly improved quality of life.

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – as evidenced and discussed with the reported outcomes anticipated from the PIONEER trial.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – this is a targeted treatment for patients with indolent systemic mastocytosis who are symptomatic and cannot be applied to the general population.

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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	HCP will need some education and training to use the technology and should be able to apply this to the clinical practice and monitor patients under clinicians who see patients with this rare disorder. There are no concomitant treatments needed, specialist equipment and monitoring is using routine current laboratory tests. Diagnostic confirmatory testing for the presence of the C-KIT D816V (using a sensitive ccPDR method) is carried out via the HMDS services and routine longterm VAF monitoring has not yet been reviewed in ISM patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the	Patients should have assessments of their symptoms and have a symptom burden that impacts on their ability to carry out activities of daily living / QOL and be on optimised minimum 2 -3 anti mast cell mediator treatments. Symptom burden can be assessed objectively with PROs – (MC- QoL/ MAS – both validated and translated into multiple languages or ISM-SAF which was used in PIONEER currently

technology? Do these include any additional testing?	available as a research tool). Once initiated treatment – suggested monitoring should be 3 monthly in the first year and review impact of avapritinib and potential option of reducing any supportive treatments. Monitor FBC, Liver function tests, tryptase levels as a guide and symptom burden.
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?	Yes – ISM patients on the trials with targeted KIT drugs, in the UK have reported benefits and improvements in the ability to function better in their ADLs, work better and have fewer episodes of ‘reactions’ which are more manageable as well as improvement in their skin rashes – this will not be captured in the QALY formula. The abstract below involved 17 ISM patients in a clinical trial and 13 were in the PIONEER study. Abstract/Poster presented at BSH 2025 - 65th Annual Scientific Meeting;Glasgow – 27-29th April 2025) Patient Outcomes and Experiences in Clinical Trials for Systemic Mastocytosis: Insights from a Comprehensive Survey Chinnabhandara S¹, Sriskandarajah P¹, Farmer I¹, Veitch S², Oni C³, Asirvatham S¹, Ordenes K¹, Ajaegbu A¹, Olaoni T¹, Radia D¹ ¹ Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom ² Lewisham and Greenwich NHS Trust, London, United Kingdom ³ Maidstone and Tunbridge Wells NHS Trust, Maidstone, United Kingdom Introduction: Indolent systemic mastocytosis (ISM) significantly impacts patients’ quality of life (QoL) with symptoms including pruritus, anaphylaxis, gastrointestinal issues and fatigue. Traditional anti-mediator therapies often fall short for many patients. Recent studies have demonstrated significant efficacy of targeted KIT D816V inhibitors: PIONEER trial with Avapritinib and the SUMMIT trial with Bezucastinib. We conducted a survey to explore our ISM patients’ experiences whilst on trial, views on symptom management, QoL and the challenges faced whilst on trial. Methods:Patients with ISM enrolled in the PIONEER and SUMMIT clinical trials were invited via email to complete online survey. Implied consent was obtained for collecting anonymized data. Data collected included demographics, clinical details (e.g., tryptase levels, C-KIT mutation), QoL ratings, symptom burden and anti-mediator use. Results:Seventeen patients were invited, with a 94% response rate (16/17). Median age range was 45–54 years with female predominance (81.2%). 43.7% worked full-time, 18.7% part-time, 12.5% retired and 56% had caregiving responsibilities. All patients had ISM confirmed on bone marrow (BM) biopsy, tryptase >20 µg/L (range: 28-230 µg/L) and were C-KIT positive. Median time from diagnosis to trial enrolment was 5 years. ISM had severely impacted QoL in 87.5% and finances in 50%. 56.2% used four or more anti-mediators (H1/H2 antihistamines, mast cell stabilisers and corticosteroids) while 31.2% used three. Common symptoms included anaphylaxis, bowel symptoms, skin involvement, allergies, fatigue and brain fog. Key motivations for trial participation included severe symptom burden (87.5%), altruism (43.7%), clinician recommendations (43.7%) and provision of financial support (6.2%). Median trial duration was 15.5 months. The most bothersome symptoms disappeared in 31.2%, significantly improved in 56.2% and showed no improvement in 12.5%. Overall, 75% reported improved QoL from trial participation. However, challenges included work pressures (31.2%), personal life disruptions (31.2%), persistent symptoms (25%), and travel issues for trial visits (12.5%). Despite these challenges, all participants recommended trials to other ISM patients with encouraging statements such as “It is worth doing for the potential improvement to your everyday life and you could be helping future patients to have a much better standard of health.” Conclusion: These ISM patients reported substantial positive benefits from participating in trials with improved symptoms and QoL for the majority. However, addressing challenges such as logistical burdens and persistent symptoms could enhance patient experiences.

	These insights highlight the positive impact targeted therapies for symptomatic ISM patients and need for continued support in clinical research.
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 – I do consider the technology to be innovative and will make a positive impact on health related benefits as is a targeted treatment which has shown benefit in the PIONEER trial as discussed in section 6 but also from clinical experience with managing 13 patients recruited on that trial in the UK and seeing the clinical / psychological improvement on these patients whilst on the treatment. The technology has the potential to be disease modifying in the longterm and current available treatments as symptomatic / supportive.
16a. Is the technology a 'step-change' in the management of the condition?	Yes – it is a definite 'step change' for all the reasons discussed earlier.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes- the improved management of a constellation of symptoms due to mast cell mediator release by targeting the clonal mast cells and reducing the mediator release and mast cell disease burden which is more effective than a combination of anti-mast cell mediator treatments which manage symptoms not disease burden.
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?	Generally reported as well tolerated by patients in the PIONEER trial on the 25mg od dose. The majority of treatment related adverse events reported were grades 1-2 and noted in approximately 15% of patients – peri-orbital and peripheral oedema, headache, diarrhoea, nausea, arthralgia, fatigue, altered taste sensation and change in hair colour (whiter). These were mostly manageable with supportive medication if needed and some also reported in the placebo cohort. There were some mild transient changes in liver transaminases at grade 1. Patients in general did not feel these outweighed the benefits they were experiencing.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Technology not available in clinical practice

18a. If not, how could the results be extrapolated to the UK setting?	UK setting extrapolation for this technology is a challenge as there is no current UK registry for ISM patients, however , there have been 2 reported audits: 2023/2025 presented at the American Society of Haematology Annual Meeting. A Snapshot Audit of Symptom Burden in Patients with Indolent Systemic Mastocytosis Utilising the ISM-SAF © within a UK Centre of Excellence: Guy's and St Thomas' NHS Foundation Trust Scott Veitch,Susan Asirvatham,Priya Sriskandarajah,Chandan Saha,Clare Oni,Clive Grattan, Deepti H. Radia <i>Blood</i> (2023) 142 (Supplement 1): 4579.https://doi.org/10.1182/blood-2023-188777 A multicentre UK snapshot audit of symptom burden in patients with indolent systemic mastocytosis utilising the ISM-SAF © Shyamala Chinnabhandara, Sneha Fernandes, Rory FD Morrice, Mahmoud Hassan, Rashmi Chandrashekar, Susan Asirvatham, Jonathan Lambert, Chun Teh, Frances Wadelin, Clive Grattan, Scott Veitch, Deepti Radia <i>Blood</i> (2025) 146 (Supplement 1): 7313. https://doi.org/10.1182/blood-2025-7313 Summary: 101 ISM patients audit;4 UK centres. Conclusion: This is the first UK audit to verify the impact of symptom burden on quality of life, 28.6% of patients having to adjust their working practice due to their ISM. A significant proportion of patients, 40.5% had TSS ≥28 and required two or more anti-mediator therapies. This compares to the original audit (36%), indicating a substantial unmet need in many patients receiving currently available standard therapies. These patients may benefit from treatment with tyrosine kinase inhibitors, presently accessible only through clinical trials in the UK.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Most important outcomes: Improvement of symptom burden – and this was measured using ISM-SAF on a continuous basis and was primary outcome which was met. Safety – side effect profile. This was reported and mostly grade 1-2 adverse events and manageable on a dose of 25mg od.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcomes/ secondary end points were looking at disease burden parameters – tryptase levels, mast cell disease burden on bone marrow biopsies and C-KIT variant allele fraction (VAF) and these showed decrease in disease burden and potential disease modifying impact in the longer term but needs longer follow up and possible improvement in bone health indices for osteopenia/ osteoporosis. A small cohort of patients with high disease burden evidenced by higher tryptase levels. BM mast cell disease burden and a higher C-KIT VAF responded to 25mg avapritinib initially but reached a plateau with increase on symptoms and tryptase levels and benefitted from an increase in avapritinib dose to 50mg od.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is more data presented in abstracts and longer term follow up data being published that will be important. There is also ‘real world’ data that is being shared as avapritinib has been approved for ISM in the USA/Europe -since 2023.

21. How do data on real-world experience compare with the trial data?	Avapritinib improves disease control and quality of life in patients with indolent systemic mastocytosis: First results of the real-world evidence study AVATAR ; Pyatilova, Polina et al. Journal of Allergy and Clinical Immunology, Volume 155, Issue 2, AB428 RATIONALE: Indolent systemic mastocytosis (ISM) is driven by KIT D816V mutation. Avapritinib, a KIT D816V inhibitor, has been recently approved for ISM treatment. While clinical trials have shown its efficacy and safety, real-world data is lacking. METHODS: ISM patients with uncontrolled disease (mastocytosis control test, MCT < 13), were enrolled. Symptom severity, quality of life (QoL), disease control and burden were assessed before treatment (w0), at week 4 (w4), 12 (w12) and 24 (w24). RESULTS: As of October 2024, Avapritinib treatment was initiated in 17 ISM patients. Treatment was well-tolerated in 15 (88%) patients reported here. The median age was 55 years, 60% female, all presented with skin involvement, 47% had osteoporosis, 20% had splenomegaly, and 40% reported anaphylaxis. Avapritinib significantly improved QoL, with median MC-QoL score decreasing from 61 at baseline to 33 at w4 ($p < 0.001$) and 17 at w24. Median MCT score increased from 7 to 15 at w4 ($p < 0.001$) with a stable score of 16 at w24, indicating achievement of disease control (MCT $\geq$ 13). Basal serum tryptase (BST) median value decreased from 53 at w0 to 42 at w4, and to 6 ng/mL by w24 ($p < 0.001$). All patients reported a continuous improvement of skin involvement, i.e., decrease in the number of lesions, color intensity, and absence of flushing episodes. CONCLUSIONS: Avapritinib 25mg daily showed significant improvement in QoL, disease control, and BST reduction as early as 4 weeks after treatment in ISM patients in a real-world setting.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that I am aware of
22b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• 40 - 50% patients with ISM have significantly impaired quality of life and debilitating symptoms • Current treatments are symptomatic only and in upto 40-45% of patients are inadequate • Patients can need upto 7-8 combinations of anti mast cell mediator treatments and still have a poor quality of life • Avapritinib in a potent selective drug which targets the C-KIT D816V mutation driving the clonal disease in ISM • Avapritinib has been shown to be effective in significantly improving symptom burden and QOL in ISM patients (PIONEER trial)

Thank you for your time.

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Your privacy

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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.

About you

1. Your name	
2. Name of organisation	British Society for Immunology Clinical Immunology Professional Network
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – (completing sections 1-5) A specialist in the treatment of people with this condition? Yes – (Completing further sections)
5a. Brief description of the organisation (including who funds it).	The BSI-CIPN is a professional network hosted within the British Society for Immunology, a learned society. The BSI-CIPN is an integrated and impactful professional network for individuals working within clinical immunology. The network includes over 160 professionals working in the clinical immunology field, including clinical immunologists, allergists, healthcare scientists, pharmacists and specialist nurses. The BSI-CIPN is funded through the British Society for Immunology, which has a range of income streams which can be viewed in our 2024 annual report here. The BSI-CIPN also has some ringfenced funding as a result of a merger with the UK Primary Immunodeficiency Network in 2022.
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.	None

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.)	
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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	No treatments only symptomatic therapies
9a. Are any clinical guidelines used in the 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.)	Highly variable and seen across haematology, immunology and dermatology specialties.
9c. What impact would the technology have on the current pathway of care?	This would provide the first treatment option and so could be used when symptoms are not controlled with antihistamines, na cromoglicate etc
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	New
10a. How does healthcare resource use differ between the technology and current care?	This would be an additional cost but it may then be possible to reduce symptomatic treatments but these are cheap
10b. In what clinical setting should the technology be used? (For example,	Specialist clinics

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Protocol development
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?	No – lifespan usually not affected. But quality of life will be likely improved
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?	no

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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult as require knowledge of side effects of drug and monitoring. Hence think should be started in specialist clinics.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start: poorly controlled symptoms despite standard therapy Stop: Trial off treatment could be considered if well controlled symptoms, tryptase normal but this is not known
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?	Likely to improve ability to work and improve ability to socialise as less reactions or fear of anaphylactic like reactions.

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 it is the first treatment for Indolent SM
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?	Yes
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?	GI side effects including nausea common. Can affect white blood counts

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes would be compatible.

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?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	na
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	na
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	na

21. How do data on real-world experience compare with the trial data?	We don't know yet

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to specialist clinics / transport costs etc
22b. Consider whether these issues are different from issues with current care and why.	More monitoring required

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

1 of 11

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Thursday 12 March 2026**. 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, 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: Treating indolent 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
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 indolent systemic mastocytosis? ☐ A specialist in the clinical evidence base for indolent 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 moderate to severe indolent systemic mastocytosis?	The main aim for treatment for moderate to severe indolent systemic mastocytosis is to improve quality of life by managing symptoms, complications, and preventing progression.

Clinical expert statement

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The management of symptoms is a major goal; one of the biggest challenges is the unpredictable nature of symptom flares. The symptoms of ISM can be extremely debilitating; patients can experience persistent and severe itching, flushing, skin burning and stinging, abdominal pain and diarrhoea, nausea and indigestion, headaches, fatigue and brain fog, dizziness, bone and muscle pain. These can be exacerbated by things such as stress, a gentle walk, being unwell, some pain relievers, and alcohol. There is also a cosmetic aspect – the typical rash of ISM may affect trunk, limbs, and sometimes head and neck, and it can be very unsightly and embarrassing. The prevention of complications is also important. Half of adults with ISM will experience anaphylaxis, which is life-threatening (ISM is a strong risk factor for death from anaphylaxis) so improvement in this is potentially very significant. About 30% of patients develop osteoporosis, with a consequent risk of fractures, so treatment may reduce this risk. Finally, treatment would ideally prevent progression. While generally ISM has a near-normal life expectancy, there is a small but real risk of progression to advanced systemic mastocytosis (AdvSM). Treatment with tyrosine kinase inhibitors (midostaurin and avapritinib) are licensed and commissioned for AdvSM and they are effective, so early treatment with TKIs may prevent progression of ISM (this is speculation – I'm not sure there is evidence yet).
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)	The biggest immediate impact of the disease on patients is the impairment in quality of life. Patients can withdraw from social, occupational, and personal activities due to exacerbation of symptoms. A clinically significant treatment response in this context would be a reduction in symptom scores or improvement in quality of life (these would generally parallel each other but may not always be synonymous). In particular patients may be able to begin participation in activities they enjoy (work, social, personal) that they are currently unable to do.

Clinical expert statement

	A “clinically significant” improvement in symptom scores is hard to quantify as it may depend on the symptom spectrum of the individual patient. In some patients an improvement of symptoms overall might be significant, and for others an improvement in their worst symptom might be significant even if other symptoms persist. For others they may have had to stop participation in activities (some patients I have have reduced work hours or even taken early retirement purely due to their condition. One patient enjoyed walking and hiking but can’t even walk to the end of the street without being debilitatingly symptomatic.) There are no biomarkers that correlate with the impact of the disease.
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe indolent systemic mastocytosis?	The major unmet need in ISM is a treatment option that actually has a direct effect on mast cells, as current treatments (below) are for symptom management by way of blocking only a few of the hundreds of mast cell mediators.
11. How is moderate to severe indolent 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 no UK/NHS guidelines for the management of ISM. However, the majority of clinicians would manage the condition in a similar way as the treatment options are very limited. The usual “maintenance” treatment pathway for symptoms would be: - Regular non-sedating H1 antihistamines, above the licensed dose - Occasionally sedating H1 antihistamines if required for nocturnal symptoms - Leukotriene antagonists (e.g. montelukast) - H2 antihistamines (e.g. famotidine) - Proton pump inhibitors for reflux/indigestion/peptic ulceration Beyond those treatments some unlicensed medications are used: - Sodium cromoglycate (a mast cell stabiliser) - Ketotifen (a first-generation antihistamine with some mast cell stabilising effect) - UV therapy was previously used but due to the 4 to 8-fold increased risk of skin cancer this is rarely used now

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	- Omalizumab (anti-IgE) has some evidence although in my experience has not been helpful As-required treatment: - Adrenaline autoinjectors for anaphylaxis - Anti-diarrhoeal medications (e.g. loperamide) - Pain relief for bone pain (may be limited as patients may not tolerate anti-inflammatory medications or opiates) - Very occasionally corticosteroids (either topical or oral) for flares It should be noted that some medications used (e.g. first-generation antihistamines, ketotifen, tricyclic antidepressants) have long-term side effects including potential increase in dementia risk. In my experience the use of H1 and H2 anti-histamines, proton pump inhibitors, and sometimes sodium cromoglycate can manage symptoms effectively in about 75% of cases; those not responding to those treatments rarely respond to anything else that's added. The technology would be very helpful in that group of cases where those treatments are insufficient.
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)	In my clinical practice I review stable asymptomatic patients with ISM annually, and on average 6-monthly where symptoms are mild, and 3-monthly where symptoms are moderate-severe; blood tests are repeated every 6-12 months and DEXA every 3 years. I expect avapritinib would increase the review frequency initially to monitor for adverse effects and blood tests, but once stable if symptoms are improved the review frequency may be less. It would only be prescribed in a specialist clinic, with monitoring either by the specialist or in a shared-care agreement with primary care. There would be no additional resources or training required.

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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?	ISM has a near-normal life expectancy, so I wouldn't expect it the technology to increase length of life significantly. However, it may reduce the risk of progression to AdvSM with associated morbidity/mortality (I'm not sure there is evidence for this yet but it is plausible). I very much expect the technology to increase health-related quality of life more than current care, as it is disease-modifying rather than purely symptomatic.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no major groups for whom it would be more or less effective.
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 may be some concomitant treatments required (e.g. to manage side effects like nausea or oedema) although these would not be routinely required. There will be additional monitoring tests although these are widely available and not complex, and as patients become stable the frequency will likely reduce.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Monitoring tests will likely be similar to the existing product license for AdvSM.
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	Participation in activities may not be captured as the measures used involve the biological aspects (spots, itching, flushing, brain fog) but not factors such as embarrassment, ability to go shopping, engage in leisure activities, participation in sport, ability to work or study, and limitations on sexual intimacy. All of these can be affected but I don't think the instruments capture this (and it is arguably more important than the other measures anyway).

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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?	The technology itself (tyrosine kinase inhibitor) is not innovative, but the use in ISM is an enormous step forward. Until now we have only had symptomatic treatment for mediator release – and only then really antihistamines and leukotrienes with weak unlicensed/off-label mast cell stabilisers – and these are woefully inadequate to treat the very significant symptoms that some people with ISM get. This would really be a step-change in management.
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?	The major side effects of the technology that I have encountered (with limited personal experience of its use) are low platelets, nausea/diarrhoea, and swelling. Reduced platelets (under 50) has been associated with bleeding, but monitoring would usually detect the reduction and the dose may be modified/withheld. Diarrhoea and nausea are usually manageable symptomatically, and oedema may require treatment. None of these has has a significant effect on QOL in my experience, but there may be. In those cases dose reduction would likely be helpful, and a minority may need to stop.
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?	I think the trials do reflect the UK setting, but another source of evidence would be the use in Europe and the US for this indication (symptomatic ISM).

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21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real-world data from the use in Europe/US for this indication.
22. How do data on real-world experience compare with the trial data?	I expect it to be similar, although I expect some clinicians may use reduced doses when patients' symptoms are fully controlled, rather than persisting with higher doses that may not be needed.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • 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.	None

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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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

ISM is a disease for which current treatments are only symptomatic.

ISM can be extremely symptomatic and cause a very significant impact on quality of life, including participation in usual activities

Avapritinib is a step-change in management for which there is evidence of benefit, and experience from use In Europe US

Monitoring will be straightforward and not involve complicated/unusual tests

Many patients will derive benefit, and some may be able to manage on reduced doses

Thank you for your time.

Your privacy

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

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Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Thursday 12 March 2026**. 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, 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: Treating indolent 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 Deepti H Radia
2. Name of organisation	UKMasto.org
3. Job title or position	Haematology Consultant
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 indolent systemic mastocytosis? ☒ A specialist in the clinical evidence base for indolent 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.	N/A

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8. What is the main aim of treatment for moderate to severe indolent systemic mastocytosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Improve symptoms and QOL and prevent progression or further disability due to mast cell mediator release. ISM is the most common subtype of systemic mastocytosis (SM) which is a clonal haematological neoplasm driven in the majority of patients (> 95%) by the <i>KIT</i> D816V. Patients with ISM can often experience longterm multiple symptoms that can have a significant and negative impact on their ability to function, carry out activities of daily living or need adjustments made at home / work to enable them to function leading to a poor quality of life. Symptoms are systemic and unique to patients and can effect their skin (80% have a rash or variable clinical cosmetic impact and itching/ flushing or can urticate depending on triggers which lead to release of mediators – pro- inflammatory- from mast cells). Symptoms can affect the GI tract leading to nausea, vomiting, abdominal pain, bloating and diarrhoea and or constipation, allergic type reactions affecting the respiratory systems – upper respiratory tract, musculoskeletal and also neurocognitive effects as these mediators cross the blood brain barrier – leading to difficulty in focus/ concentration, memory problems, inability to carry out instructions, calculations and word recognition – impairing functional ability at work and at home and impacting quality of life. Some patients present with and suffer from anaphylactic reactions and these can be life threatening in their own right especially if no trigger is identified. Avapritinib is an oral, highly selective and potent inhibitor of D816V mutated <i>KIT</i> so targets the mutation that drives this disease. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200339 J Gotlib et al. Avapritinib vs Placebo in Indolent Systemic Mastocytosis. 23rd May 2023/ NEJM Evid 2023 ;2(6). The PIONEER trial (NCT03731260: part 1/2/3) to assess the efficacy and safety of avapritinib 25mg once daily (potent direct C-KIT inhibitor) in adult indolent systemic mastocytosis patients with moderate to severe symptoms, on at least 2 anti-mast cell mediator optimised therapies with persistent symptoms demonstrated a significant improvement with decrease in overall symptom burden and improvement in quality of life for those patients on avapritinib vs best available supportive care. Randomisation was 2:1 (avapritinib vs placebo both with best supportive care).

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Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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	Total number of patients enrolled 212 (141 on avapritinib and 71 placebo arm). TSS scores ≥ 28 (range 0-110) based on ISM-SAF©. Primary end point was mean change in TSS based on a 14 day average of patient reported severity of 11 symptoms. Secondary end points : reductions in serum tryptase, blood <i>KIT</i> D816V variant allele fraction (VAF $\geq 50\%$ and $\geq 30\%$), reduction in bone marrow mast cells ($\geq 50\%$) -all 3 reflecting any changes in mast cell disease burden and quality of life measures. Results from baseline to week 24 showed: Median duration of treatment part 2 was 5.6 months (24.1 weeks) for both groups – 96% avaprtinib pts and 93% on placebo continued on part 3 open label extension to receive 25mg avapritinib. • TSS scores decreased by 15.6 points in avapritinib treated patients (95% CI -18.6 to -12.6) vs 9.2 points in the placebo cohort (95% CI- -13.1 to -5.2); $P < 0.003$. • 76/141 patients on the avapritinb arm had a 54% (45%-62%) reduction in serum tryptase compared to placebo 0/71(0%) achieved $\geq$ reduction. • Avapritinib was generally well tolerated with commonest side effects reported being oedema, increases in ALP – transient, mostly grade 2 and manageable. Very few treatment discontinuations due to adverse events. • Mean (SD) change in the most severe symptom reported by patients was -2.2 on avapritinib arm vs -1.4 in the placebo arm. • 80/118 (68%) avapritinib arm patients had $\geq 50\%$ decrease in <i>KIT</i> D816V VAF vs 4/63 (16%) in the placebo arm. $P < 0.001$ • 56/106 (53%) had a $\geq$ reduction in bone marrow mast cell burden vs 13/57 (23%) in the placebo arm.$P < 0.001$. • BSC usage was reduced / discontinued in 24% of the avapritinib arm of patients vs 13% in placebo cohort by week 24. • BSC increase use was noted in 11% of patients on placebo vs 8% avapritinib arm. • QOL improvements were noted avapritinib vs placebo over 24 weeks as measured by SF-12 physical scores increased by 20% vs 12%

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	SF-12 mental health scores increased by 12% vs 6% EQ-VAS scores increased by 19% vs 5% MC-QoL scores decreased by 34% vs 18% After the 24 week crossover in the open label part 3 (26 pts) completed an additional 24 weeks and there was a mean TSS improvement in those who were on the placebo. 4yr follow up data presented at AAAAI February 2026 – confirms continued maintained improvement of symptoms with associated improvement in QOL with no new safety concerns..
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)	ISM patients have symptoms that impact on their quality of life as a result of the clonal mast cells releasing mediators. These can have local effects on the organs infiltrated or distant/ systemic affects. The mast cell disease burden is variable and can be low in some patients who can still suffer from significant symptoms depending on their individual triggers. Patients with ISM do not have any end organ damage typically resulting in organomegaly – enlarged liver/ spleen size or any abnormal blood counts so these cannot be used to measure any clinical responses unlike patients with advanced systemic mastocytosis. As we are assessing symptom burden and improvement this should be the clinical response measured to confirm benefit of treatment with avapritinib. Decrease in symptom burden and severity, improvement in overall quality of life as a result, decrease in those patients who suffer from anaphylactic reactions as easily documented but this accounts for a small proportion of ISM patients, decrease in use of best supportive / additional anti mediator treatments needed / used over time. Other measures which are important but not usually measured outcomes formally would be ability to ability to perform tasks which we not possible at baseline – increase working hours, ability to spend more time with family/ socialise/be less dependent on carers or support from family to manage activities of daily living. The PIONEER trial demonstrated that using a 2 week daily average of the ISM-SAF form improvements in the TSS scores for patients of avapritinib 25mg od vs those in the placebo arm and across all 11 domains over 24 weeks. This improvement was also shown in the additional QOL assessments forms – MCQoL, EQ-VAS, SF-12 physical and mental health scores. Currently there is no standardised form utilised uniformly in clinical practice as patients will

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	present to different disciplines and there can be different QOL/ PROs available. So a trend in improvement over time of symptoms, improvement and change in QOL, reduction in supportive medications would be an important clinical significant outcome rather than a fixed – pre-determined percentage.
10. In your view, is there an unmet need for patients and healthcare professionals in moderate to severe indolent systemic mastocytosis?	Yes, there is an unmet need for patients who suffer with extremely symptomatic ISM and have unpredictable reactions to mast cell mediator release despite optimisation of the currently available best supportive combination of anti-mast cell mediator treatments. Patients can have a debilitating responses/ triggers or unknown triggers leading to inability to function, have an extremely poor quality of life and require care or support to manage. This targeted KIT D816V inhibitor directly targets the clonal mast cells, leading to decrease in the mast cell mediator release and mast cell disease burden; reduced tryptase, reduced visible skin lesions, reduced bone marrow mast cell numbers and quantifiable mutation levels (VAF) and hence not only has an impact in reducing symptom burden but potential longterm disease modifying effects. For patients on the PIONEER trial avapritinib has made a significant improvement above and over standard therapies. Patient -Reported Outcomes and Provider Perceptions of Systemic Mastocytosis: Results From the PRISM Study. Massimo Triggiani et al. Clinical & Experimental Allergy, 2025; 55:784–794https://doi.org/10.1111/cea.70101784 Methods: PRISM (funded by Blueprint Medicines Corporation) was composed of two independent surveys: a 119-item patient survey on diagnosis, symptom burden, quality of life (QoL) and work impact; and a 103-item healthcare provider (HCP) survey on approaches to SM diagnosis and management. Results: Data were evaluated from 540 patient respondents from Italy (n = 136), France (n = 112), the UK (n = 101), Germany (n = 83), Spain (n = 64), Austria (n = 26) and Switzerland (n = 18). 237 pts had ISM and 50 were UK patients. Patients reported a high symptom burden and reduced physical functioning and mental health due to SM, despite taking, on average 5-6 medications. 38% reported experiencing anaphylactic episodes within the previous year. With 21% having 5 or more episodes of anaphylaxis. 43% of ISM patients reported that SM impacted their ability to work, 24% needing to reduce hours and 17% needing to stop work completely.

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	Yes – an unmet need for healthcare professionals who manage these rare patients in their specialties/ with multidisciplinary input and support as best as they can – access for the symptomatic patients to avapritinib with education regarding the side effect profile although generally well tolerated and managing these patients over the longterm.
11. How is moderate to severe indolent 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?	Current treatment options are all supportive and symptom management based to deal with the fallout of mast cell mediator release. Avoidance of triggers if identified – some food products, medications, environmental triggers (temperature changes). Then the mainstay is anti-mast cell mediator medications in variable combinations depending on response. These include anti histamines (anti H1 and anti H2 receptor antagonist – short and long acting: Loratadine, Cetirizine, Piriton, Fexofenadine, Ketotifen, Nizatidine, Cimetidine or Famotidine), mast cell stabiliser – Sodium cromoglycate. These medications are often needed in higher doses than recommended in the BNF for ISM patients. Tricyclic anti-depressants for low mood, pain management – Amitriptyline, Gabapentin. Patients who have anaphylaxis associated with wasp stings maybe treated with wasp venom immunotherapy which is recommended as longterm treatment in patients with a confirmed diagnosis of ISM currently. These patients with anaphylaxis will auto inject with adrenalin pens to manage their anaphylactic episodes and some may need corticosteroids post episode if severe or more than 1 adrenalin injection. Omalizumab – anti IgE maybe available for patients with chronic urticaria associated with their ISM. PUVA treatment may be available for patients with a significant rash – skin involvement of their mast cells which is cosmetically disturbing and/or leading to itching/ flushing. The impact cosmetically on skin lesions is transient whilst being treated. For severe reactions, corticosteroids maybe required for short term in some patients and low dose in some patients to control or reduce flares in some patients. To manage the 30% risk of osteopenia / osteoporosis supplementation with Vitamin D/ Calcium or treatment with bisphosphonates is required.

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	For very severely affected patients who have been refractory to multiple anti mast cell mediator therapies – some form of cytoreductive treatment (off label use) maybe considered: Cladribine/Interferon alpha/ hydroxycarbamide. Clinical trials are recently available for patients if they can take part. No current UK clinical guidelines available and are being worked on this year with a writing group established under the haematology BCRI working group. Valent P et al. Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice. J Allergy Clin Immunol Pract. 2022 Aug;10(8):1999-2012.e6. doi: 10.1016/j.jaip.2022.03.007. Epub 2022 Mar 25. PMID: 35342031. USA NCCN guidelines are available as a guide: Systemic Mastocytosis, Version 3.2024JNCCN.org Volume 22 Issue 2D June 2024 Majority of patients with ISM that are symptomatic are under the care of haematologists/ dermatologists and some allergists/immunologists. There is no UK defined pathway of care but historically patients who are treated with TKIs have usually been under the care of haematologists as there is experience with managing these targeted drugs. I would anticipate more centres will have a multi-disciplinary approach to diagnose and manage these patients in a secondary care setting and this is evolving.
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)	Currently avapritinib is not available / or in use in routine NHS clinical practice. Technology should be used in secondary care setting and specialist clinics – currently most SM patients are seen by haematologists with an interest in myeloproliferative neoplasms, however, this usually involves the management of advanced systemic mastocytosis. ISM patients will be under the care of dermatologists, allergists, immunologists and haematologists across the UK and the primary clinician will depend on the ‘set up’ in that area. There will need to be introduction into clinical practice / pharmacy of the technology and education of all clinicians and patients. There will be anticipated increase in OPA reviews of

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What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	patients who start avapritinib initially and then once established 4-6 monthly reviews. These symptomatic patients are likely to be seen more frequently than those who are minimally symptomatic and in annual reviews so should not be a significant increase in OP activity longterm. Investment to introduce technology will mainly be a focus on education and training to recognise symptom management and potential side effects. No additional facilities/ equipment is necessary.
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 – as already discussed in section 6 with the results of the PIONEER trial and outcomes. Life expectancy for ISM patients is ‘normal’ compared with an aged-matched population and so there is not an anticipated further increase in length of life but more significantly improved quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – this is a targeted for patients with indolent systemic mastocytosis who are symptomatic and cannot be applied to the general population.
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,	HCP will need some education and training to use the technology and should be able to apply this to the clinical practice and monitor patients under clinicians who see patients with this rare disorder. There are no concomitant treatments needed, specialist equipment and monitoring is using routine current laboratory tests. Diagnostic confirmatory testing for the presence of the C-KIT D816V (using a sensitive ccPDR method) is carried to via the HMDS services and routine longterm VAF monitoring has not yet been reviewed in ISM patients.

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factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients should have assessments of their symptoms and have a symptom burden that impacts on their ability to carry out activities of daily living / QOL and be on optimised minimum 2 -3 anti mast cell mediator treatments. Symptom burden can be assessed objectively with PROs – (MC-QoL/ MCAS – both validated and translated into multiple languages or ISM-SAF which was used in PIONEER (currently available as a research tool). This PRO should be used in conjunction with overall clinical impression of the impact of the SM on the patients’ QOL and a holistic approach to overall improvement in QOL should be applied in assessing efficacy. Once initiated treatment – suggested monitoring should be 3 monthly in the first year and review impact of avapritinib and potential option of reducing any supportive treatments. Monitor FBC, Liver function tests, tryptase levels as a guide and symptom burden. From clinical experience with the trial – the majority of patients have variable and continued improvement in responses over time.
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?	Yes – it is a definite ‘step change for all the reasons and will make a positive impact on health related benefits as is a targeted treatment which has shown benefit in the PIONEER trial as discussed in section 6. Yes – ISM patients on the trials with targeted KIT drugs, in the UK have reported benefits and improvements in the ability to function better in their ADLs, work better and have fewer episodes of ‘reactions’ which are more manageable as well as improvement in their skin rashes – this will not be captured in the QALY formula.(Abstract/Poster presented at BSH 2025 - 65th Annual Scientific Meeting;Glasgow – 27-29th April 2025)
- 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?	

Clinical expert statement

Patient Outcomes and Experiences in Clinical Trials for Systemic Mastocytosis: Insights from a Comprehensive Survey

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Introduction:

Indolent systemic mastocytosis (ISM) significantly impacts patients' quality of life (QoL) with symptoms including pruritus, anaphylaxis, gastrointestinal issues and fatigue. Traditional anti-mediator therapies often fall short for many patients.

Recent studies have demonstrated significant efficacy of targeted KIT D816V inhibitors: PIONEER trial with Avapritinib and the SUMMIT trial with Bezuclastinib. We conducted a survey to explore our ISM patients' experiences whilst on trial, views on symptom management, QoL and the challenges faced whilst on trial.

Methods:

Patients with ISM enrolled in the PIONEER and SUMMIT clinical trials were invited via email to complete online survey. Implied consent was obtained for collecting anonymized data. Data collected included demographics, clinical details (e.g., tryptase levels, C-KIT mutation), QoL ratings, symptom burden and anti-mediator use.

Results:

Seventeen patients were invited, with a 94% response rate (16/17). Median age range was 45–54 years with female predominance (81.2%). 43.7% worked full-time, 18.7% part-time, 12.5% retired and 56% had caregiving responsibilities. All patients had ISM confirmed on bone marrow (BM) biopsy, tryptase >20 µg/L (range: 28-230 µg/L) and were C-KIT positive. Median time from diagnosis to trial enrolment was 5 years. ISM had severely impacted QoL in 87.5% and finances in 50%.

56.2% used four or more anti-mediators (H1/H2 antihistamines, mast cell stabilisers and

	corticosteroids) while 31.2% used three. Common symptoms included anaphylaxis, bowel symptoms, skin involvement, allergies, fatigue and brain fog. Key motivations for trial participation included severe symptom burden (87.5%), altruism (43.7%), clinician recommendations (43.7%) and provision of financial support (6.2%). Median trial duration was 15.5 months. The most bothersome symptoms disappeared in 31.2%, significantly improved in 56.2% and showed no improvement in 12.5%. Overall, 75% reported improved QoL from trial participation. However, challenges included work pressures (31.2%), personal life disruptions (31.2%), persistent symptoms (25%), and travel issues for trial visits (12.5%). Despite these challenges, all participants recommended trials to other ISM patients with encouraging statements such as “It is worth doing for the potential improvement to your everyday life and you could be helping future patients to have a much better standard of health.” Conclusion: These ISM patients reported substantial positive benefits from participating in trials with improved symptoms and QoL for the majority. However, addressing challenges such as logistical burdens and persistent symptoms could enhance patient experiences. These insights highlight the positive impact targeted therapies for symptomatic ISM patients and need for continued support in clinical research.
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?	Generally reported as well tolerated by patients in the PIONEER trial on the 25mg od dose. The majority of treatment related adverse events reported were grades 1-2 and noted in approximately 15% of patients – peri-orbital and peripheral oedema, headache, diarrhoea, nausea, arthralgia, fatigue, altered taste sensation and change in hair colour (whiter). These were mostly manageable with supportive medication if needed and some also reported in the placebo cohort. There were some mild transient changes in liver transaminases at grade 1. Patients in general did not feel these outweighed the benefits they were experiencing.

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?	Currently the technology not available in clinical practice. UK setting extrapolation for this technology is a challenge as there is no current UK registry for ISM patients, however , there have been 2 reported audits: 2023/2025 presented at ASH- American Society of Haematology as abstracts/posters looking at UK patients with ISM and symptom burden. Publication Number: 7313 Submission ID: abs25-7684 Title: A multicentre UK snapshot audit of symptom burden in patients with indolent systemic mastocytosis utilising the ISM-SAF © A multicentre UK snapshot audit of symptom burden in patients with indolent systemic mastocytosis utilising the ISM-SAF © Shyamala Chinnabhandara, Sneha Fernandes, Rory FD Morrice, Mahmoud Hassan, Rashmi Chandrashekar, Susan Asirvatham, Jonathan Lambert, Chun Teh, Frances Wadelin, Clive Grattan, Scott Veitch, Deepti Radia Journal: Blood <i>Blood</i> (2025) 146 (Supplement 1): 7313. https://doi.org/10.1182/blood-2025-7313 Background: Indolent systemic mastocytosis (ISM) is a rare clonal haematological neoplasm driven by KIT D816V mutation in 95% of cases leading to uncontrolled proliferation and accumulation of mast cells. It can be associated with debilitating mast cell mediator symptoms affecting skin, gastrointestinal (GI) tract, neurocognitive function, bone turnover and anaphylaxis which significantly impact quality of life. Treatment is limited to symptom management and there are no approved targeted therapies available in the UK. The ISM symptom assessment form (ISM-SAF ©; Taylor et al.[2021]) is a validated and effective symptom assessment tool developed specifically for ISM patients focusing on 11 symptoms over a 24- hour recall period: bone pain, abdominal pain, nausea, skin spots, itch, flushing, fatigue, dizziness, brain fog, headache and diarrhoea. Each symptom is scored on a scale from 0 (no symptom) to 10 (worst imaginable symptom). We present UK-wide data of 101 patients from four centres as a re-audit of a previous single-centre cohort of 76 patients by Veitch et al.[2023]. Methods: Adults with

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ISM diagnosed on a bone marrow biopsy and/or extracutaneous tissue as per World Health Organization classification were identified between June 2023 to July 2025 retrospectively. 101 patients participated across four centres in the UK [Guy's and St Thomas' Hospital (68), University College London Hospital (14), St James University Hospital (10) and Nottingham University Hospital (9)]. Over a four-week period, patients were invited to complete the ISM SAF © by telephone or in person. Demographic, clinical data, anti-mediator therapy and anaphylaxis history were also collected. This study also focused on the impact of ISM on bone health, quality of life and working hours. All consultations were conducted by a haematology clinician in each institute. Results: Of the 101 patients, median age at diagnosis was 46 years (range 11-76) with female predominance (62.4%). Median time to ISM diagnosis was 4.1 years (range 0.1-55.6). Median latest serum tryptase was 37.5 mcg/L (range 7.9-196; n=99) and 2 patients had levels >200 mcg/L. 88 patients (87.1%) were noted to have the KIT D816V mutation (6.9% KIT D816V-negative, 4.9% not available and 0.99% equivocal). Bone marrow trephine mast cell infiltrate ranged between 2-70%. 30 patients (29.7%) had a history of anaphylaxis at least once in their lifetime and 6.6 % (n=2) reported using an adrenaline autoinjector within the last 12 months. The median total symptom score (TSS) was 31 (range 0-90). The highest scoring symptom was fatigue (mean score 5.1) followed by skin spots (mean score 4), flushing (mean score 3.7), brain fog (mean score 3.5) and itch (mean score 3.4). 55 patients (54.5%) had a TSS ≥ 28 and 35 patients (34.7%) had TSS of ≥ 42 indicating moderate and severe disease, respectively. 89 patients had a DEXA scan of which 16 patients (17.9%) had osteoporosis, 32 (35.9%) had osteopenia. 10 of 16 patients (62.5%) with osteoporosis were on bisphosphonate therapy. ISM is a recognised contributor to bone density loss and bone pain. Among patients with moderate disease (TSS ≥ 28), 41 patients (74.5%) were on ≥ 2 medications (needing combinations of up to 5 different classes of anti-mast cell mediator therapies). Medications included H1 antihistamines (n=89), H2 antihistamines (n=49), proton pump inhibitors (n=22), sodium cromoglicate (n=23), montelukast (n=12), oral corticosteroid (n=1) and omalizumab (n=3). 18 patients (17.8%) had to take time off their work in the last year due to ISM related symptoms (range 1-90 days) and 11 patients (10.8%) reported reducing their working hours or retiring early because of ISM. Conclusion: Our re-audit highlights an additional 101 ISM patients across 4 centres in the UK with significant real-world symptom

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burden. This aligns with findings from the previous single-centre audit and the PRISM study (M. Triggiani et al. [2025]). This is the first UK audit to verify the impact of symptom burden on quality of life, 28.6% of patients having to adjust their working practice due to their ISM. A significant proportion of patients, 40.5% had TSS ≥ 28 and required two or more anti-mediator therapies. This compares to the original audit (36%), indicating a substantial unmet need in many patients receiving currently available standard therapies. These patients may benefit from treatment with tyrosine kinase inhibitors, presently accessible only through clinical trials in the UK.

A Snapshot Audit of Symptom Burden in Patients with Indolent Systemic Mastocytosis Utilising the ISM-SAF © within a UK Centre of Excellence: Guy's and St Thomas' NHS Foundation Trust Scott Veitch, Susan Asirvatham, Priya Srisankarajah, Chandan Saha, Clare Oni, Clive Grattan, Deepti H. Radia

Blood (2023) 142 (Supplement 1): 4579.

<https://doi.org/10.1182/blood-2023-188777>

Background: Indolent systemic mastocytosis (ISM) is a rare, clonal haematological neoplasm driven by the KIT D816V mutation in up to 95% of cases. It is characterized by a debilitating, heterogenous and unpredictable symptom burden due to mast cell mediator release among patients. Treatment is limited to symptom management with no approved targeted therapies in the UK. The Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) (Taylor et al. [2021]) is a validated symptom assessment tool developed specifically for ISM patients focusing on 11 symptoms over a 24-hour recall period: bone pain, abdominal pain, nausea, skin spots, itch, flushing, fatigue, dizziness, brain fog, headache and diarrhoea. Each symptom is scored on a scale from 0-10. To date, there has not been any published UK data examining symptom burden in ISM patients. Subsequently we assessed symptom burden utilising the ISM-SAF in our patient cohort at Guy's and St Thomas' Hospital. Method: All adult ISM patients who had a routine outpatient appointment between May 2022 and May 2023 were identified retrospectively. Over a four-week period, patients were invited to complete the ISM-SAF by telephone or in person. Additionally we collected demographic data, clinical data, anti-mediator

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therapy, anaphylaxis history and the impact of SM on their work and quality of life. All consultations were conducted by a clinical member of the mastocytosis team. Results: 95 adult patients with ISM were identified within our database, of which 76 consented to take part in this study. There was a slight female predominance (41% male; 59% female) and the median age at diagnosis was 46 years (range 21 - 78). Median time to ISM diagnosis was 4.6 years (range 0.5-18.5). Median serum tryptase was 35 mcg/L (range 9-632). 66 patients (88%) were noted to have the KIT D816V mutation (6% D816V-negative, 6% not available). The median Total Symptom Score Abstract #188777 A Snapshot Audit of Symptom Burden in Patients with Indolent Systemic Mastocytosis Utilising the ISM-SAF within a UK Centre of Excellence: Guy's and St Thomas' NHS Foundation Trust © 1* 2* 2* 2* 3* 2* 1 2 3 © © © 03/10/2023, 20:20 Abstract #188777 <https://ash.confex.com/ash/2023/cop/papers/viewonly.cgi?password=747824&username=188777> 2/7 (TSS) was 24 (range 0-110). The highest scoring symptoms were fatigue (mean score 4.66), skin spots (3.97), brain fog (3.43) and itch (2.83). 33 patients (43%) had a TSS ≥ 28 which is the threshold determined by psychometric analysis to identify patients with moderate to severe symptoms, and is used for screening in clinical trials (Shields et al. [2023]). 46 patients (61%) were prescribed ≥ 2 anti-mediator therapies; at the time of the study, current therapies included H1 antihistamines (n=64), H2 antihistamines (n=28), proton pump inhibitors (n=20), sodium cromoglycate (n=18), montelukast (n=12), corticosteroid (n=5) and omalizumab (n=1). 12 patients (16%) were on a bisphosphonate. The number of patients with both a TSS ≥ 28 and on ≥ 2 anti-mediator therapies was 27 (36%). 30 patients (39%) reported a history of anaphylaxis at least once in their lifetime while 12% (n=9) reported using an adrenaline autoinjector within the last 12 months. There was no statistically significant correlation between TSS and serum tryptase (Pearson correlation coefficient $r = -0.08$, $p = 0.48$). Some patients reported having to reduce their working hours, needing adjustments or retiring early due to symptoms attributed to their ISM diagnosis. Conclusions: Our data demonstrate a significant real-world symptom burden among the ISM patient cohort within the UK Mastocytosis Centre of Excellence and reflect the findings of other centres, in particular fatigue being the most severe symptom (van Anrooij et al. [2016]; Mesa et al. [2022]). The ISM-SAF is an effective tool for capturing a snapshot of symptom severity and has utility in the outpatient setting. Importantly, we found over one third of patients

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	in our centre had a TSS ≥ 28 and were on ≥ 2 antimediation therapies, meaning they could potentially be eligible to access tyrosine kinase inhibitors within the clinical trial setting. Most important outcomes: Improvement of symptom burden – and this was measured using ISM-SAF on a continuous basis and was primary outcome which was met. For patients with significant skin/ cutaneous disease burden that suffered because of the cosmetic concerns and itching, flushing of skin symptoms the skin lesions markedly improved and this was visible – leading to a major improvement in quality of life. Safety – side effect profile. This was reported and mostly grade 1-2 adverse events and manageable on a dose of 25mg od. 4yr follow up presented at AAAAI in February 2026 has not reported any new side effects. Surrogate outcomes/ secondary end points were looking at disease burden parameters – tryptase levels, mast cell disease burden on bone marrow biopsies and C-KIT variant allele fraction (VAF) and these showed decrease in disease burden and potential disease modifying impact in the longer term but needs longer follow up and possible improvement in bone health indices for osteopenia/ osteoporosis. A small cohort of patients with high disease burden evidenced by higher tryptase levels. BM mast cell disease burden and a higher C-KIT VAF responded to 25mg avapritinib initially but reached a plateau with increase on symptoms and tryptase levels and benefitted from an increase in avapritinib dose to 50mg od.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None that I am aware of.

22. How do data on real-world experience compare with the trial data?	There is more data presented in abstracts and longer term follow up data being published that will be important. There is also ‘real world’ data that is being shared as avapritinib has been approved for ISM in the USA/Europe -since 2023. 21 Avapritinib improves disease control and quality of life in patients with indolent systemic mastocytosis: First results of the real-world evidence study AVATAR Pyatilova, Polina et al. Journal of Allergy and Clinical Immunology, Volume 155, Issue 2, AB428 Avapritinib improves disease control and quality of life in patients with indolent systemic mastocytosis: First results of the real-world evidence study AVATAR Polina Pyatilova, MD1 , Philipp le Coutre2 , Leonie Herzog1 , Melba Mu- ~noz1 , Nicole Nojarov1 , Pascale Salameh, PharmD PhD3 , Sebastian Schröder2 , Frank Siebenhaar, PD Dr Med1 ; 1 Institute of Allergology, Charite – Universitätsmedizin Berlin, Berlin, Germany, 2 Department of Oncology and Hematology, Charite-Universitätsmedizin Berlin, Berlin, Germany, 3 Lebanese University. RATIONALE: Indolent systemic mastocytosis (ISM) is driven by KIT D816V mutation. Avapritinib, a KIT D816V inhibitor, has been recently approved for ISM treatment. While clinical trials have shown its efficacy and safety, real-world data is lacking. METHODS: ISM patients with uncontrolled disease (mastocytosis control test, MCT < 13), were enrolled. Symptom severity, quality of life (QoL), disease control and burden were assessed before treatment (w0), at week 4 (w4), 12 (w12) and 24 (w24). RESULTS: As of October 2024, Avapritinib treatment was initiated in 17 ISM patients. Treatment was well-tolerated in 15 (88%) patients reported here. The median age was 55 years, 60% female, all presented with skin involvement, 47% had osteoporosis, 20% had splenomegaly, and 40% reported anaphylaxis. Avapritinib significantly improved QoL, with median MC-QoL score decreasing from 61 at baseline to 33 at w4 ($p < 0.001$) and 17 at w24. Median MCT score increased from 7 to 15 at w4 ($p < 0.001$) with a stable score of 16 at w24, indicating achievement of disease control (MCT > 13). Basal serum tryptase (BST) median value decreased from 53 at w0 to 42 at w4, and to 6 ng/mL by w24 ($p < 0.001$). All patients reported a continuous improvement of skin involvement,

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	i.e., decrease in the number of lesions, colour intensity, and absence of flushing episodes. CONCLUSIONS: Avapritinib 25mg daily showed significant improvement in QoL, disease control, and BST reduction as early as 4 weeks after treatment in ISM patients in a real-world setting.
23. 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	No – I don't think there are any issues with inequalities in terms of patient groups but looking forward at the UK – we need to look at patient pathways and ensure all clinicians who treat patients with ISM have the foundation of knowledge of how the symptoms burden can be assessed and when to review best supportive medications to transition to avapritinib, then monitor. This will be an education drive.

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- 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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients with indolent systemic mastocytosis have a clonal mast cell haematological neoplasm which lead to mediator release causing significant and debilitating symptoms, including life-threatening anaphylaxis, impacting adversely on quality of life.
- Current management is supportive and consists of a combination of multiple anti-mast cell mediator therapies which do not control symptoms in a large proportion of patients, highlighting an unmet need for improved treatment for these patients.
- Avapritinib is an oral, highly selective and potent inhibitor of D816V mutated *KIT* so targets the mutation that drives this disease.
- Avapritinib has demonstrated in clinical trial (PIONEER) a significant improvement with decrease in overall symptom burden and improvement in quality of life for those patients on avapritinib vs best available supportive care.
- 4yr follow up and real world evidence demonstrates continued, durable responses in patients who have access to avapritinib with transformation in patients' quality of life.

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.

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Single Technology Appraisal

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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 indolent systemic mastocytosis or caring for a patient with indolent systemic mastocytosis. 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.

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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.

The deadline for your response is **5pm on Thursday 12 March 2026**. 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 indolent systemic mastocytosis

Table 1 About you, indolent systemic mastocytosis, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with indolent systemic mastocytosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with indolent 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: Getting to know the

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	experience of other patients for 35 years and listening to them as a patient advocate. ☐ 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 indolent systemic mastocytosis? If you are a carer (for someone with indolent systemic mastocytosis please share your experience of caring for them	I was diagnosed with cutaneous mastocytosis when I was 19 and with indolent systemic mastocytosis at age 22 (though I didn't have the proper workup until that time, so likely had ISM at 19 or before). When I was first diagnosed I had a just few symptoms—some upper GI pain from hyperacidity, and a florid rash on my trunk and thighs that sometimes itched. It was shortly after my diagnosis with ISM that my symptoms started coming on more aggressively. I started on medications (the typical anti-mediator therapies) one by one as my symptoms increased and began making big changes to my daily living to try to stave off symptoms, with limited success. I spent much of my years in graduate school writing essays on my laptop on the loo because I had regular cramping and diarrhoea. I became increasingly intolerant to airborne scented products (perfumes, cleaners, others' laundry soap, air "fresheners" etc) which cause headaches, flushing of the skin and decreased cognitive function. I had been a lifeguard to earn while I was a student, but after a major episode that had me well on the way to anaphylaxis from jumping into cold water on a hot day, I stopped swimming. I began having episodes where I flushed red and had GI symptoms at work, often after lunch, and as a relatively fit person in my 20s found that I couldn't walk up a flight of stairs without stopping to catch my breath. When I also started to feel like I was going to pass out during these episodes I ended up leaving work several times via ambulance and being treated in A&E. I began to recognise a pattern around foods I was eating preceding these episodes (though allergy testing has never shown food allergies) and a very

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	stressful job was certainly feeding into these episodes. My mastocytosis doctor (one of not very many in the US with an interest in it at the time) told me about research on the biochemical link between emotional and physical stress and mast cell degranulation that helped me understand myself better, and understand the many patients I've met over the years who say that they react to stress—not just “difficult” stress, but also to happy events that make them emotional. Stress management techniques for me help a bit but can only go so far, as stress is a part of normal life. I also found, by trial an error (since the allergy tests came back normal), which foods make me feel very unwell (flushing, tachycardia, loss of cognitive function) and avoiding those (about 30) foods helps, but is severely limiting in day-to-day life, and particularly when traveling outside my normal orbit. (Alcohol causes immediate reactions, so drinking is out, but I also need to avoid when it is airborne as it makes me flush and feel unwell.) I also found that my cognitive function can be affected by airborne scented products (natural and human-made). While I can do my best to avoid the morning blast of peoples' freshly applied products on public transport, and wear a mask that can slow reactions, places like public toilets have such chemicals that can't be avoided. One of my teenagers wanted so much to smell like his peer group and use scented products and it was very difficult to have to stay firm on the no-scent rule in our house. There were certain friends of my children that I couldn't have in a carpool because of their family's choice of laundry soap. I get a laugh sometimes, when I say I haven't had a bath in 20 years (I can shower in cooler water), but soaking in a nice bath is a luxury I miss. It is not worth having to take to my bed for several hours afterward when the mast cell mediators triggered by the heat cause extreme fatigue. In the first ten years after diagnosis I had very regular cramping and diarrhoea and had circumstances where I was very close to extremely embarrassing situations. (Luckily, I had my son's travel potty with me while it hit when I was driving on a 6-

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	lane highway in America or I'd have been bare-bottomed on the side of the road.) The stories that I have heard from patients are heartbreaking: having to find an alley in a city because they couldn't get to a loo fast enough; having to stop the car to use a cow field, with the whole family in the car, and needing to put soiled clothing in the boot anyway. The cramping can be 10/10 pain (and I had 2 unmedicated births—to avoid the risk of anaesthetic, which can trigger anaphylaxis). I have less frequent cramping and diarrhoea now, but it can still come on with a combination of triggers (stress, fatigue, chemical exposure, inadvertent consumption of wrong foods or of alcohol). It is the unpredictability and the fear of being caught out that makes things so challenging and constrains patients' lives. In my 20s I also experienced chronic severe bladder pain and vulvodynia, both of which can be mast cell mediated though they are not well documented in the research literature, in part because patients aren't asked about these symptoms and don't volunteer them. These symptoms are now episodic rather than chronic, perhaps because of the trigger avoidance and effects of anti-mediator therapies. I know patients who lose urinary continence when they are having a flare of their symptoms. My professional life took a sharp turn when it became clear that my body couldn't tolerate the kind of high pressure but fulfilling job I had trained for. I decreased my hours to manage my fatigue and took less-challenging work until I eventually left the workforce. I now work on a voluntary basis for the patient charity, which allows me to adjust my workload to fit my physical constraints. I still need to control my environment and can't be certain that I will be at my best cognitively when I need it. This is what I struggle with most from an emotional standpoint. I have had osteopenia and one painful lesion on my femur since my 20s, both symptoms of mastocytosis. Given what we now know about resistance training and bone health, I am grateful to have found careful ways to move my body by attending a training class for people over 65 (I am not there yet) where I can go

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	at a slower pace and focus on strength over cardio to ensure I don't overheat or overexert. I arrange my attendance so I'm not there on the days when the cleaner comes because the cleaning products set me off, and I always know where the big fan is and turn it on myself when I start to get too hot. And I know that if I overdo it, I will need to take to the sofa for a few hours afterward. I feel I have been lucky regarding my skin spots (maculopapular cutaneous mastocytosis). My spots get raised, red and itchy due to friction (I choose fabrics carefully for trousers as my thighs are most affected), and from heat or cold or the contrast between heat and cold, but those events are time limited. Some people have constant itching, or severe flares where the itching is truly unbearable. This affects their ability to be attentive to work or school, or really to anything. I have met people who have felt suicidal over this symptom. Likewise, I feel lucky that I haven't been terrifically bothered by the way my spots look. It helps that mine are mostly are parts of my body that I am anyway inclined to keep covered. I have met many patients who have been bullied about their spots (even in adulthood, with strangers confronting them at the beach and thinking they are infectious) and feel very deeply the experience of being marked. Likewise, I feel lucky that my flares usually resolve themselves within 24 hours and don't now involve full-on anaphylaxis. The most common flare pattern for me is to begin by looking and feeling as if I am pregnant with a baby elephant. This rapid swelling of the abdomen is followed by cramping and diarrhoea, skin flushing and fatigue. I know people who keep maternity clothes to accommodate their "baby elephants" during flares. I don't tend to have nausea or headaches with my flares, though these are common, nor do I tend to itch for long. Some people have their skin go red and stay red, looking scalded during flares. One challenge that adds to the stress of ISM patients is not knowing whether the treatment for some other medical situation will set off mast cells. The most dramatic illustration of this for me took place in Tanzania, where my husband was working for

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	a time. I developed a full body rash to the anti-malarial that I had carefully tried at home under observation before the trip. With guidance from my home mastocytosis doctor, I then did a trial of another antimalarial medication in a clinic. My husband had to use two epipens on me while the doctor started fluids (and we had to make a rapid change of travel plans). My doctors and I had to negotiate our way around my mast cells for recent treatment of breast cancer: surgeries (anaesthesia, pain meds and antibiotics can all set off mast cells), radiotherapy (what creams could I tolerate? How would my skin tolerate it?), and hormone blocking medication (would it cause anaphylaxis?). I was relieved when the MDT agreed that chemotherapy wasn't needed as that's another minefield for mastocytosis patients. Patients struggle to be able to tolerate medications they need for other problems (made more difficult because with a rare disease and patient heterogeneity there isn't much research to go on). I have had ISM for my whole adult life, so in many ways I have adapted to the constraints, but I remember the freedoms of my childhood, and I mourn the career that wasn't possible. I try to feel hopeful that the new medications that I began working for in my 20s will be available to me.
7a. What do you think of the current treatments and care available for moderate to severe indolent 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 have taken more or less the same combination of medications to control symptoms since the 1990s because that's all that has been available. There have not been advances in treatment until now. (I take H1 and H2 blockers, a proton-pump inhibitor and montelukast daily and carry). I took sodium cromoglycate (a mast cell stabiliser) for about ten years before it started causing upper GI pain. While it helped some with my lower GI symptoms, the trade-off wasn't worth it. I have since tried it once during a long severe GI flare and had muscle pain and then the upper GI pain again, so I stopped again. I carry epipens wherever I go. I know that I get some benefit from my medications, because if I forget a dose, within a few hours I begin to feel very unwell. But the drugs don't address my triggers including sensitivity to things in my environment, food stress, temperature, and exertion-induced

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	reactions. My symptoms remain as well—Upper GI pain and hyperacidity, variable cognitive function, fatigue, muscle aches, bone pain, cramping and diarrhoea. b. Having been in contact with thousands of other patients over 30 years in my role as a patient advocate in the US and UK, I have heard many stories about which symptoms are not managed by the current medications. I consider myself to have moderate rather than severe ISM at this stage and with all of my constraining trigger avoidance strategies in place. Those with severe ISM have symptoms like mine (and more) with greater frequency and/or intensity and some experience anaphylaxis with regularity. I know people who have to take higher doses of H1 blockers than I do and have their cognition even more compromised. I know people who can't take montelukast because of the psychological side effects. Patients who take omalizumab to stave off anaphylaxis have found that it can sometimes trigger it either right away or after some months of use. I know people who don't tolerate medications well at all and live with the symptoms, only because they aren't as bad as the side effects of the medications for them. And there are patients like the other patient you're hearing from at the committee meeting who found no benefit from BSC medications.
8. If there are disadvantages for patients of current NHS treatments for moderate to severe indolent systemic mastocytosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As described above, the current treatments for ISM can have many side effects: In particular: H1 antihistamines can all be sedating (even the less sedating ones), and the anti-cholinergic effects can have consequences for example for eye health when taken over tens of years. People worry about whether they might cause dementia over time, given the recent studies suggesting a connection. H2 antihistamines may not be well tolerated. I took Ranitidine for 25+ years before it was pulled from the market because of concerns that it might cause some cancers. And many patients find the remaining H2 options less effective while hoping they are at least safer. Proton pump inhibitors can cause stomach polyps with long term use, and can increase the risk of fractures, kidney disease, c diff infections etc. Since they would

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	be used long term there is a higher risk of these more significant side effects. They can also cause unpleasant short term side effects including nausea and dizziness. Anti-Leukotriene medications: Montelukast can cause mental health problems. Zafirlukast was pulled from the UK market and there is no other anti-leukotriene drug available now in the UK. Sodium cromoglycate: In my case side effects caused me to stop taking it. It needs to be taken 4x a day, 30 minutes before food and 2 hours after food for maximum effect, as it isn't well absorbed. Some people find it works better if it is put in hot water and stirred very vigorously rather than taken by capsule, a ritual that is highly inconvenient (having done it for ten years). Even with a cocktail of medications, "success" is moderate blocking of two or three mast cell mediators out of literally hundreds that mast cells can release, or not very effective mast cell stabilisation. None of these treatments addresses the underlying proliferation of mast cells and none gives us any expectation that it might prevent progression to more aggressive disease over time, nor does anti-mediator therapy prevent osteoporosis, a long-term consequence that I started worrying about in my 20s. Additional medications that we listed in our response to the scoping include: omalizumab (sometimes causes anaphylaxis in patients with mastocytosis, and can cause flu-like symptoms, and requires a hospital visit), osteoporosis treatments (very little research done about what works in mastocytosis as compared to in menopausal women, but the side effects of those meds include jaw necrosis and GI pain), oral corticosteroids (side effects of long term use are well documented and include osteoporosis and adrenal insufficiency), phototherapy (only works temporarily, and not in everyone, and increases the risk of skin cancer), dermivate under occlusion (can only be used for a short time due to risk of skin atrophy and only addresses skin lesions and the effect is temporary).
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	a. I have not taken avapritinib myself. I have gotten feedback (including responses to our survey that was used for the charity's submission) from UK patients who participated in the trials, and have seen feedback from patients

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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	in our charity's Facebook group and in the online group I help moderate of ~2000 people who have SM with a strong presence from the US, where avapritinib is already on the market. b. The advantages that patients report vary but I frequently hear/read the words "normal" to describe how patients feel. From a day-to-day perspective, being able to live normally without all of the constraints I've described and you will have read about elsewhere, is an enormous improvement in quality of life. It's difficult to be more specific since each patient's set of symptoms vary, but in the trial one of the endpoints measured was improvement in whichever symptom was worst for the patient. Those improvements were significant (statistically and in terms of QOL) no matter what the worst symptom was. c. Avapritinib is a complete change of approach, as compared to the existing treatments which can only try to hold back the tidal wave of effects of mast cell mediators. Avapritinib gets at the underlying issue—the proliferation of mast cells. It does not cause sedation. We don't think it is going to cause dementia like anti-cholinergic medications. We have no reason to expect it to cause the issues ranitidine might have caused. I have not heard of anyone having depression unlike with montelukast, nor the particular issues that are enumerated above about the other medications that I don't take.
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 read about the side effects in the trial population—eye oedema, nausea, fatigue, change in hair colour. I've read about them resolving in many patients after a month or so, but not in all (and I suppose some of those might choose to stop taking it if the side effects feel worse than the symptoms). I find it reassuring that the side effects resolved in patients who stopped the drug, and that there were no serious adverse events in the trials. Risk wise, I understand it should not be used by people who are pregnant, and I suppose we don't know about effects in people who

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	might get pregnant in future and there should be appropriate counselling around that.
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	We know that the population of people with ISM is quite diverse in presentation of their disease. Symptoms vary, triggers vary and responses to existing medications vary. As far as I know, we don't have any particular populations which we know would benefit more (or less) than others from avapritinib, but that's something we may learn in the future.
12. Are there any potential equality issues that should be taken into account when considering moderate to severe indolent systemic mastocytosis and avapritinib? 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.	An equality issue that I return to every time I write something for NICE is a geographical/services issue. People who live farther from specialist centres may be less likely to get access to avapritinib because their doctors may not hear about it or have the experience to judge who is suitable. I have a concern that doctors who are not familiar with the ISM-SAF might be less likely to make the effort to get access for their patients if they think using the tool is too difficult. We know from the PRISM study, which looked at healthcare providers' and patients' views of systemic mastocytosis that there is a gap between patient perceptions of the effect of ISM symptoms on the QOL (more unwell) than doctors' views (a bit less unwell) so I worry that inexperienced providers may not make it available when it would be appropriate.
13. Are there any other issues that you would like the committee to consider?	No.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The effects of living with this chronic, episodic, unpredictable disease are not limited to the unpleasant physical manifestations; people with moderate to severe ISM live circumscribed lives in an effort to control the currently uncontrollable.
- The existing treatments poorly manage the symptoms of people with moderate to severe ISM (or they wouldn't score as moderate to severe on QOL tools); the side effects of BSC are difficult for many patients and decrease QOL.
- Avapritinib is a dramatic step change from the way that treatment has been approached since I was diagnosed in 1992; finally there is a medication that gets at the underlying problem, addresses multiple symptoms at once, and may well prevent progression, and will decrease the demand for emergency care.
- Some people who have taken avapritinib for ISM describe their lives now as normal; this medication has the potential to return a good number of ISM patients to lives that are full physically, socially and professionally.
- Even for those who do not have a full resolution of symptoms with avapritinib or who experience side effects, the improvement of symptoms will bring their QOL from pretty miserable (EQ5-D levels are worse than in lung cancer) to a lot better. That's of value to us all.

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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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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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 indolent systemic mastocytosis or caring for a patient with indolent systemic mastocytosis. 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.

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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.

The deadline for your response is **5pm on Thursday 12 March 2026**. 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 indolent systemic mastocytosis

Table 1 About you, indolent systemic mastocytosis, current treatments and equality

1. Your name	Michelle Shave
2. Are you (please tick all that apply)	☒ A patient with indolent systemic mastocytosis? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with indolent systemic mastocytosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The UK Mastocytosis Support Group (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

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	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 indolent systemic mastocytosis? If you are a carer (for someone with indolent systemic mastocytosis please share your experience of caring for them	At around the age of 13 I started to develop a rash on my legs every time I did PE, dance or any physical activity at school. The rash gradually became more frequent and more intense/itchy/painful. The rash then spread to the rest of my body when triggered, eventually leaving permanent spots on my legs. Not only was this extremely debilitating, meaning I could no longer participate in normal activities for a young girl, but it was also extremely stressful to have to navigate trying to hide the rash and the discomfort at such a delicate time in my life. Over the next few years, the “attacks” became more frequent and progressed to not only a rash but more symptoms at each attack. I started to experience symptoms such heart palpitations, intense heat, extreme itchiness, and a much more prominent and wider spread rash. I experienced light-headedness and my blood pressure would drop dangerously low. I was later told that I was having anaphylaxis and issued with EpiPens I believe it was by the time I was in my very early 20s the attacks for me became part of my “normal daily life” and to myself, friends and family it would be known as “I was having a heat rash”. I did not know what was wrong with me. I had been diagnosed with urticaria pigmentosa, and was given lots of different tablets over the years, none of which helped, apart from the antihistamines perhaps taking the sting off slightly. I had been told many things over the years by health professionals, that I was just having panic attacks, I was probably just allergic to something, and my mum was told to just bring me back “when there was something to be seen”. I tried very hard to hide my true emotions, as without being able to let people know what was wrong with me, as I myself didn’t know, I felt as if I was being dramatic, perhaps even bringing it on myself, especially as many times people who did not know me would say, “oh yes, prickly heat, I get that.” I simply gave up trying to make people understand, and just got on with it the best I could. Even people who

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	were close to me were not fully aware of how much it affected my life, I simply tried to navigate day to day to not have an attack, which was virtually impossible, so when I did have an attack a lot of the time I just took myself off and tried to get through it on my own. I would say my significant attacks started in my 20s. I probably could not even list all the triggers to my attacks, as there have been so many, but all of them I would consider just normal daily activities. Any form of exercise – I did try as I really wanted to be able to exercise, every time resulted in an attack. Although sometimes you do not plan to exercise as such. If I was with friends and we were say catching a bus or a train, instinctively if the bus/train is coming and you are not quite there you run, everyone would start to run, I would follow and then I would have an attack! Dancing at parties - I had to limit the time, stop, go the bathroom to splash cold water, sit down for a bit, but this would normally result in sitting/laying outside in the cold having an attack. I was young, I would mostly get looked at, ignored by adults as they would just assume I had had too much to drink or had taken drugs. The sun appearing unexpectedly – This happened on a regular occasions. I once picked my son up from preschool which was next to a park, he wanted to play for a little while. It was a fairly mild day in September and I sat under a tree whilst he played, he was 3 years and 2 months old. There were a few other adults there, none of whom I knew, they disappeared off and then all of a sudden we were on our own the sun heated up. My son was up a climbing frame and was calling for help, he then wet himself and was very upset. I was laying on the floor having an attack, I could not move to help him. My son managed to get down and get my EpiPen for me. Luckily, I have always lived close to my mum (on purpose), I managed to text her “help” and a rapid response team arrived to me very quickly. I was also 7 weeks pregnant. This is my son’s earliest childhood memory. Public transport – I used to work in London. Trains would often get cancelled. I had to wait on hot platforms and judge what train to get onto, sometimes I had to get on very busy trains otherwise I would have been there for hours. I had to time it right if I was going to have an attack, to ask someone if I could have their seat, which would

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	cause anxiety in itself. I would have to remove a much of my clothes as I could, including any socks and shoes and would just have to go through an attack. No one knew what was going on and what to do. I once got off a train at my village and the staff ran into the village to find my mum telling her that I had nearly fallen on the tracks. I had attacks regularly on station platforms, if it was getting late in the evening I was walked over as if I was a drunk. I was regularly left in very vulnerable situations. Washing – My husband removed baths from our house so that I could not be tempted, I could not have baths, or long showers, washing my hair had to be as quick as possible or in a cool shower. Getting ready to go out – This always caused me anxiety and usually ended up in an attack. On a cold day walking into a shop with heating on. I would always have to dress so that I could quickly remove layers to cool down. Housework had to be done in stages. Hoovering was particularly difficult. Cooking was also difficult. Standing next to a hot stove and the normal feeling of trying to bring a meal together with the right timings could cause anxiety and then an attack. Eating in restaurants. If the restaurant all of a sudden got busy and heated up that would cause an attack. Any situation where I felt anxious, for example, work meetings and public speaking. If I was asked a direct question this could cause an attack. I worked in the same job in London for years, I would often have attacks at work, but it became so regular, colleagues would often say things like “try not to die on us today”. I would find a quiet room or a space under a desk and just go through my attacks on the floor. I had a few ambulances sent to work and one time after there was a rumour going around that the “management” were not happy as it had cost them money and there was “nothing wrong with me”. I gave instructions to my line manager as to what I needed in an attack, I simply received an email to say it would be passed onto the first aiders. No one ever came

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	to see me, and I just continued to take myself away if was having an attack as I basically felt as if no one ever took me seriously. Medical situations. I have had surgeries in the past, once I was under anaesthesia for 8 hours, I was having a planned operation for removal of endometriosis where I ended up losing a lot of blood, later requiring a blood transfusion. No one could really tell me what really happened, but I remember coming round from the operation and being wrapped in a silver blanket shivering intensely. I have had two bowel resections, 6 fertility treatments and an ectopic pregnancy. Through all of these I felt very vulnerable and alone with my condition, not knowing if would have any bearing on the situations. I would tell medical staff about my condition and how it affected me, but I felt as if no one really listened. Getting into a hot car. I would have to turn my car on and then find shade until it had cooled down. I later taught my son how to do this for me. Any kind of stress. I opened an email telling me what secondary school my son had got into, it was not what I was expecting, this resulted in an attack and another ambulance! Picking up my children from school. I had a friend who lived near to the school, if the sun was out, I would quite regularly have to go to her house to cool down or have an attack before I went home. Watching my sons perform in any sporting activities. Sports days were hard and watching my son take a penalty on a sunny day was almost definitely an attack. I very stupidly decided to do a boot fair by myself once, I sent off at 5am, it was nice and cool. By 11am I was sitting in a field in the sun and started to have an attack. I literally threw my mobile to a man, said my passcode and the words "husband Tim, ambulance and anaphylaxis". I accidentally stuck my EpiPen in my thumb! Luckily once again the ambulance arrived very quickly, as did my sister. Holidays were definitely not as relaxing as they could have been. I actually really feel the cold and loved a nice warm holiday. I could never be alone and would have to have an umbrella. I also had to be right next to the pool so that I could get in every so often to cool down.

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	Sleeping – I would someone wake up having an attack, usually if I was hot but sometimes from anxiety. I woke up in the middle of the night having an attack in the hotel room the night before I went to the hospital to start the drug trial. My list could go on and on. If I think about whether I could have avoided some of my attacks, most definitely, but I literally would have had to stay indoors and do nothing, which I was not prepared to do. So in terms of my quality of life, I only had a quality of life because I learnt to live with having attacks, my quality of life with attacks was horrific, but to me it was normal. Normal to me was to try not to be alone and to try and avoid attacks, but just deal with them when they happened. In terms of what an attack meant they generally started with a feeling of my heart starting to race. It would rapidly increase in speed and literally feel like it was pumping out of my chest. I would also get the same feeling in my head, my head would thump and it would be like a strobe effect on my eyes, everything flashing. My whole body heat up and feel like it was on fire, I did sometimes get some intense itchiness (although I think the 6 antihistamines I was taking a day did help with this a little). My legs, arms and chest would be covered in angry red and raised spots, and my face would be bright red and was really hot. It was an overwhelming sense of doom. I had to lie down as quickly as possible to prevent fainting and as it gradually got worse, I could not move or talk and a couple of times I had what my husband described as fits. I literally had minutes to say “heat rash” to anyone around me and they would have to jump into action. I would need cool packs, cool wet towels, my EpiPen, a bowl and towels laid out in case I was sick or had diarrhoea. I would lay for about 30 minutes with this overwhelming sensation and then I would get intense cramps in my stomach and feel as if was going to be sick or have diarrhoea, which sometimes did happen. My body would then start to shake and shiver uncontrollably. I would become really cold and have to be wrapped in blankets for about another 30 minutes until I warmed up, at which time could then start to talk and move again. Once my body had recovered, I was left

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	with a pounding headache and would need to sleep for a few hours. I would then generally feel weak for the rest of the day. In term of how often this happened, I was preventing attacks daily, but full-blown attacks would happen probably 2 or 3 times a week. On the whole, I would convince people around me not to call ambulances, although I have had many called over the years. I felt like a burden. The paramedics were always amazing, but always insisted taking me to hospital, where I would spend a few hours to be told there was nothing wrong with me so I could go. This once happened in London, I had been to a show and then rushed for the last train. I ended up in an ambulance and taken to hospital. They let me out at 2 in the morning and there were no trains home and I was exhausted. These types of experiences therefore generally made me manage my attacks without calling for medical help. I generally tried to manage my attacks on my own but have been very lucky to have my husband, and have always lived close to my mum and two sisters, who I am very close with, and, especially when my sons were young, I had good friends around me. From an early age my sons had to learn how to look after me when I was having an attack, which was very scary for them. My eldest son who is now 19, remembers me having attacks from when he was 3 onwards and is now very protective of me. My husband was at work during the week and my son became that person who would always be there for me, and also for his brother who is nearly 4 years younger than him. He shielded his brother from what was going on, not only looking after me when I had an attack but also taking his brother off so that he did not have to witness my attacks from a young age like he did. My son and I are naturally extremely close, but unfortunately this has had a negative impact on him in terms of the anxiety that he suffers. The impact on my family and friends was also really significant, they had to be either there for me and my sons, at a drop of a hat for every waking moment, which was extremely stressful for them and naturally they were very worried for me. I had an overwhelming feeling of being a constant burden.

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	I did of course have a medical bracelet, but in terms of what happened to me and how quickly, if I did not have someone with me who knew what to do it was very difficult, as a stranger could not possibly know what was happening and once I got to a certain stage I could not talk. Around 5 years ago I went to my dermatologist at the Hospital, he referred me to [REDACTED]. I was very quickly seen and was told that I was most likely suffering with ISM. I underwent some tests including a bone marrow biopsy and was told the diagnosis was confirmed. I was asked if I would like to be considered for a trial for Avapritinib. Of course, although very anxious, I was delighted that there was some hope for me to lead a normal life. Once on the trial I was not aware if I was on the drug or placebo, but very quickly my attacks stopped. I have not had one attack since in nearly 5 years. My skin completely cleared up, and I only take an occasional antihistamine if I am doing any intense exercise, but if I am honest this is probably more psychological. Despite not having attacks I found it hard to live normally to start with, I was always worried that I would still have attacks. I sometimes also can feel quite down thinking of what I went through and how I coped day to day, I still worry about if I did not have Avapritinib how I would cope now I know what it's like to be "normal", but I try to let all of that go and enjoy every day being free from the horrific symptoms that I endured all those years. I do not know what I would do without Avapritinib I simply could not go back to living my life how I used to. I can honestly say that Avapritinib has been totally life changing for me and for my family and friends. I no longer have any symptoms and have not had any side effects from the drug that I am aware of.
7a. What do you think of the current treatments and care available for moderate to severe indolent systemic mastocytosis on the NHS?	I believe that the current treatments and care for those with ISM is much like it was for myself before Avapritinib. I have only recently met a few patients with ISM at my hospital appointments, in the waiting room, and I am a member of the Facebook support group, and my impression is that many patients are given lots of different drugs to deal with lots of different symptoms/aspects of the disease, with no real benefit at all. Patients are still suffering with symptoms and feel as if there is

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7b. How do your views on these current treatments compare to those of other people that you may be aware of?	nowhere to turn. It is very depressing and lots of patients feel very alone with their disease.
8. If there are disadvantages for patients of current NHS treatments for moderate to severe indolent systemic mastocytosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I am aware that many patients have to take a lot of different drugs, which sometimes they cannot get hold of. From my own personal experience and I think that of others, the drugs don't even help, patients just take them in the hope that they are doing something. Patients also have adverse reactions to some of the drugs. The drugs can make you feel very tired, particularly the antihistamines.
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	Avapritinib has literally changed my life. I can dance at parties, I have joined a choir, (which I definitely could not do before, especially standing on a stage in front of people). I can do exercise. I have completed a lifelong desire to be able to run (I completed the Couch to 5k and am now working towards doing my first half marathon). I now work self-employed as I am confident to be totally independent. But the biggest advance is that I can just be me, on my own and not feel as if I must be looked after by anyone or a burden to everyone around me. I feel that I now live a normal life doing all of the normal daily tasks that most people take for granted, I can take a walk on my own, sit in the park or on the beach in the sun without worrying, I can whizz around doing the housework, I can take a call whereby someone might need me to do something quickly and I can just do it, I can run to the shops, enjoy eating out. I can have a nice warm shower or bath, feel normal emotions, such as being excited or even scared without the fear of an attack. I can just enjoy a normal day without having to plan every move depending on the weather, my clothing, my emotions and what might or might not happen, which was just impossible in the past. The most important advantage is that I don't have to wake up every day not knowing if and when I am going to have my next attack, and the complete

Patient expert statement

	overwhelming sensation that what if the next attack will be the one that goes really wrong, and which one of my loved ones would have to witness it.
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 can honestly say that I have not had one side effect from taking Avapritinib that I am aware of. I haven't really spoken to anyone else who is on the drug so am not aware if anyone else has suffered any side effects.
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 believe that my triggers of heat, exercise and stress are only a few of the triggers that can affect patients with ISM. Many patients also have attacks from eating certain foods and from smells and from some medications. These patients may also benefit from Avapritinib, and also be able to live a normal life.
12. Are there any potential equality issues that should be taken into account when considering moderate to severe indolent 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	I believe that pregnant women are not allowed to take Avapritinib, other than that I am not aware of any potential issues.

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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?	N/A.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- ISM can totally ruin a person's day to day life.
- ISM ruins the lives of those caring for someone with ISM.
- If a person has ISM they deserve to be helped to live a normal life.
- ISM may be rare, but it is very real.
- Avapritinib has changed my life.

Thank you for your time.

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in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd., in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Nigel Armstrong acted as project lead and health economist on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Huiqin Yang also acted as project lead and systematic reviewer on this assessment and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Mabel Wieman and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott and Dan Lin acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Keith Nockels and Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AdvSM	Advanced systemic mastocytosis
AE	Adverse event
AIM	American Initiative in Mast Cell Diseases
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ASM	Aggressive systemic mastocytosis
BM	Bone marrow
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CI	Confidence interval
CON	Confidential
CONSORT	CONsolidated Standards Of Reporting Trial
COVID-19	Coronavirus disease 2019
CR	Complete response
CS	Company submission
DCO	Data cut-off
DoR	Duration of response
DoT	Duration of treatment
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECM	Established clinical management
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimension 5-Level questionnaire
EU	European Union
EUR	Erasmus University Rotterdam
FE	Fixing errors
FV	Fixing violations
GI	Gastrointestinal
HCHS	Hospital and community health services
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HTA	Health Technology Assessment

ICER	Incremental cost-effectiveness ratio
IgE	Immunoglobulin E
Incr.	Incremental
ISM	Indolent systemic mastocytosis
ITC	Indirect treatment comparison
ITT	Intention-to-treat
kg	Kilograms
K-M	Kaplan Meier
KSR	Kleijnen Systematic Reviews
LLD	Lower limit of detection
LOCF	Last Observation Carried Forward
LS	Least squares
LY	Life-years
MAF	Mutant allele fraction
Max	Maximum
MC	Mast cells
MCAR	Missing completely at random
MCL	Mast cell leukaemia
MC-QoL	Mastocytosis Quality of Life questionnaire
MCS	Mental Component Summary
MD	Mean difference
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Multiple Imputation
Min	Minimum
MJ	Matters of judgment
MMRM	Mixed Models for Repeated Measures
MSAF	Mastocytosis Symptom Assessment Form
MS2D2	Mastocytosis Symptom Severity Daily Diary
N/A	Not applicable
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NMB	Net monetary benefit
Non-AdvSM	Non-advanced systemic mastocytosis
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PCR	Polymerase chain reaction
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

PP	Per-protocol
PPI	Proton-pump inhibitors
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISM	Perceptions Realities and Insights on Systemic Mastocytosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen ultraviolet
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
REMA	Spanish Network on Mastocytosis
RP2D	Recommended Phase 2 dose
RWE	Real-world evidence
SAE	Serious adverse event
SAF	Symptom Assessment Form
SC	Subcutaneous
SD	Standard deviation
SDT	Symptom-directed therapy
SE	Standard error
SF-12	12-item Short Form Survey
SLR	Systematic literature review
SM	Systemic mastocytosis
SmPC	Summary of Product Characteristics
SoC	Standard of care
SSM	Smouldering systemic mastocytosis
TA	Technology Assessment
TECH-VER	TECHnical VERification
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TSS	Total symptom score
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC+	University Medical Centre+
US	United States
VAF	Variant allele frequency
VAS	Visual analogue scale
WHO	World Health Organization
WTP	Willingness-to-pay

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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. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the Key Issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-Key Issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's Key Issues

Table 1.1: Summary of Key Issues

ID6578	Summary of issue	Report Sections
1	Uncertainty as to the population who would be eligible for avapritinib	2.1
2	Uncertainty as to whether dose escalation for avapritinib will occur in clinical practice	2.2 and 3.2.4
3	Uncertainty as to what is regarded as SDT or ECM	2.3
4	Uncertainty as to the generalisability of SDT in the PIONEER trial	3.2.4
5	Variability in efficacy of avapritinib in PIONEER by ISM-SAF domain	3.2.6
6	Appropriateness of using the ISM-SAF TSS to classify disease severity	4.2.2
7	Questionable generalisability of the company's modelled patient population to UK clinical practice	4.2.3
8	Likely under-estimation of avapritinib treatment duration and potential inappropriateness of 24-week stopping rule	4.2.6
9	Potential disease progression is not fully reflected in the model, SDT long-term effectiveness assumed to be equal to baseline	4.2.6
10	Progression to SSM and AdvSM is unequal in both arms, inducing a mortality benefit for patients on avapritinib	4.2.6
11	Utility benefit for avapritinib responders	4.2.8
12	Approach for the estimation of the ISM health state utilities	4.2.8
13	Resource use benefit for avapritinib responders	4.2.9
AdvSM = advanced systemic mastocytosis; EAG = External Assessment Group; ECM = established clinical management; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; SDT = symptom-directed therapy; SSM = smouldering systemic mastocytosis; TSS = total symptom score; UK = United Kingdom		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival [OS]) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, according to the company's original submission, the technology is modelled to affect QALYs by:

- Increased duration in the mild disease state (██████ QALYs, █████ the total incremental QALYs)
- Reduced duration in the severe disease state (██████ QALYs, █████ of the total incremental QALYs)

Overall, the technology is modelled to affect costs by:

- Increased drug acquisitions costs of avapritinib (██████, █████ the total decreased costs)
- Decreased drug acquisitions costs of SDT (██████ █████ the total decreased costs)

The modelling assumptions that have the greatest effect on the ICER according to the company are:

- Tyrosine kinase inhibitor (TKI) usage 0% (increased the ICER by █████)
- 50% resource use reduction (decreased the ICER by █████)
- Time on treatment 5 years (decreased the ICER by █████)
- Midostaurin usage -5% (increased the ICER by █████)

1.3 The decision problem (DP): summary of the EAG's Key Issues

The DP addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key Issue 1: Uncertainty as to the population who would be eligible for avapritinib

Report Section	2.1
Description of issue and why the EAG has identified it as important	Moderate to severe symptoms based on a minimum mean TSS of ≥ 28 on the ISM-SAF is part of the eligibility criteria for the PIONEER trial, which is used by the company to define the DP population. However, EAG and company clinical expert opinion suggests that this instrument is not universally used in UK clinical practice. Also, some patients with mild disease according to the ISM-SAF might be eligible in clinical practice for avapritinib if the disease affecting only one system e.g. the skin is regarded as severe.
What alternative approach has the EAG suggested?	The EAG has only requested clarification on the applicability of the ISM-SAF in UK clinical practice, which confirmed the possible discrepancy between PIONEER and clinical practice.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this Key Issue?	Further evidence on the effect of avapritinib on moderate to severe disease, which would be categorised as mild using the ISM-SAF could be presented. Alternatively, those patients with mild disease according to the ISM-SAF, or those with moderate to severe disease, but only affecting one system, could be excluded.

Report Section	2.1
CE = cost effectiveness; DP = decision problem; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; TSS = total symptom score; UK = United Kingdom	

Table 1.3: Key Issue 2: Uncertainty as to whether dose escalation for avapritinib will occur in UK clinical practice

Report Section	2.2 and 3.2.4
Description of issue and why the EAG has identified it as important	The marketing authorisation for avapritinib is the 25 mg dose, and this was used in the economic model. However, dose escalation to 50 mg was permitted in PIONEER part 3, and one of the EAG clinical experts stated: “There was a [REDACTED] grade 3 reaction rate with 50mg, rising to [REDACTED] with 100mg (esp nausea, headache, diarrhoea). These are similar symptoms to those of ISM anyway, and patients may therefore find this an acceptable risk. For patients with very high symptom burden this would therefore be an acceptable risk, and the dose remains much lower than doses used for SM. It may therefore have been more helpful if the patients with dose escalation hadn’t been excluded.” This does therefore raise a question as to whether dose escalation would occur in clinical practice, and consequently the generalisability of the trial data and the applicability of the economic model to UK clinical practice.
What alternative approach has the EAG suggested?	The company provided, on EAG request, the results of those patients with no dose escalation, which showed little difference to the whole population. However, those [REDACTED] who dose escalated might have had worse outcomes if they had not dose escalated.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this Key Issue?	There is a need for clarification as to whether dose escalation could occur in UK clinical practice, which would then inform the generalisability of PIONEER and the economic model.
CE = cost effectiveness; EAG = External Assessment Group; ISM = indolent systemic mastocytosis; SM = systemic mastocytosis; UK = United Kingdom	

Table 1.4: Key Issue 3: Uncertainty as to what might be regarded as SDT or ECM

Report Section	2.3
Description of issue and why the EAG has identified it as important	The comparator is described as ECM without avapritinib in the NICE scope, and SDT in the DP. Figure 11 in the CS lists the following treatments in the final branch of the therapeutic pathway: interferon-alpha, omalizumab, cladribine, TKIs and BSC. In the PIONEER trial, the term SDT is generally used, but in some cases interchangeably with BSC. This raises questions as to what the comparator should be, and whether that in PIONEER matches it. The EAG clinical experts suggested that SDT is the appropriate comparator i.e. those patients in receipt of SDT would be eligible for avapritinib. They seemed to rule out interferon-alpha, cladribine and TKIs, although the company includes them in the economic model comparator.
What alternative approach has the EAG suggested?	The EAG requested clarification, to which the company responded that ECM, SDT and BSC are essentially equivalent, with omalizumab included.

Report Section	2.3
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this Key Issue?	Further data or clinical expert opinion might be sought as to precisely which treatments are currently used to treat patients with moderate to severe ISM in UK clinical practice in order to assess the generalisability of PIONEER and to inform the basket of treatments in the economic model.
BSC = best supportive care; CE = cost effectiveness; CS = company submission; DP = decision problem; EAG = External Assessment Group; ECM = established clinical management; ISM = indolent systemic mastocytosis; NICE = National Institute for Health and Care Excellence; SDT = symptom directed therapy; TKI = tyrosine kinase inhibitor; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's Key Issues

Table 1.5: Key Issue 4: Uncertainty as to the generalisability of SDT in the PIONEER trial

Report Section	3.2.4
Description of issue and why the EAG has identified it as important	The percentages of patients receiving each type of SDT in the PIONEER trial differ to some degree with clinical expert opinion, both company and EAG based. In particular, omalizumab use is about 10% in the trial, but stated to be no more than 5% by the clinical experts. Larger discrepancies occur between PIONEER and the EAG clinical experts for omeprazole, montelukast, and cromolyn sodium. This raises a question as to the generalisability of PIONEER.
What alternative approach has the EAG suggested?	The EAG requested a comparison between PIONEER and clinical practice, which prompted the company to present their clinical expert opinion.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this Key Issue?	Once it is established what should be the comparator i.e. clinical practice for those patients eligible for avapritinib (see Key Issue 2), the generalisability of PIONEER can be better understood.
CE = cost effectiveness; EAG = External Assessment Group; SDT = symptom-directed therapy	

Table 1.6: Key Issue 5: Variability of efficacy of avapritinib in PIONEER by ISM-SAF domain

Report Section	3.2.6
Description of issue and why the EAG has identified it as important	Overall, the results of PIONEER showed that there were better outcomes with avapritinib 25 mg than placebo, including statistically significant differences in change in overall symptom score (ISM-SAF TSS), and proportion achieving both $\geq 30\%$ and $\geq 50\%$ reduction in TSS. However, treatment effects were not observed consistently across all ISM-SAF symptom domains, with improvements primarily driven by the skin domain, suggesting potential heterogeneity of effect across symptoms. This might be a concern if patients become eligible for avapritinib because their symptoms are predominantly not skin-related or those of the skin not the most severe. Indeed, the baseline characteristics of Part 2 of PIONEER show that a high percentage of patients (about 80%) have

Report Section	3.2.6
	symptoms that are not skin-related, although it is unclear as to the degree of overlap between the various domains.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Given that improvement in treatment effects was primarily driven by the skin domain, the use of avapritinib in the subgroup of patients with severe skin domain might be more cost-effective. Further evidence on subgroup analysis is required.
What additional evidence or analyses might help to resolve this Key Issue?	The company could present the percentages of patients in PIONEER who would be regarded as having severe disease according to the skin domain, but mild according to the neurocognitive or gastrointestinal domains of the ISM-SAF. These percentages could then be compared with those of patients in UK clinical practice. Subgroup analysis by these domain categories might also be considered to see if the treatment effect is lower for any patients with severe skin, but only mild neurocognitive or gastrointestinal symptoms.
CE = cost effectiveness; EAG = External Assessment Group; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; TSS = total symptom score; UK = United Kingdom	

1.5 The cost effectiveness evidence: summary of the EAG's Key Issues

A full summary of the cost effectiveness (CE) evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential Patient Access Schemes (PASs) in a confidential appendix. The Key Issues in the CE evidence are discussed in Tables 1.7 to 1.15.

Table 1.7: Key Issue 6: Appropriateness of using the ISM-SAF TSS to classify disease severity

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The EAG is concerned that there may be a mismatch between the disease severity classification in the company's model structure and UK clinical practice. This may have resulted in patients being classified as having mild disease (i.e. not eligible for avapritinib) in the company's model, while these would potentially be treated with avapritinib in clinical practice.
What alternative approach has the EAG suggested?	The EAG requested justification for using ISM-SAF TSS to classify disease severity and consideration of alternative outcomes.
What is the expected effect on the CE estimates?	Unclear
What additional evidence or analyses might help to resolve this Key Issue?	Additional analyses using an approach for the classification of patients' disease severity that is more closely aligned with UK clinical practice.
CE = cost effectiveness; EAG = External Assessment Group; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; TSS = total symptom score; UK = United Kingdom	

Table 1.8: Key Issue 7: Questionable generalisability of the company's modelled patient population to UK clinical practice

Report Section	4.2.3
Description of issue and why the EAG has identified it as important	The EAG questions the generalisability of the company's modelled patient population to UK clinical practice, because: 1) The ISM-SAF threshold (i.e. TSS ≥ 28) may not fully capture the heterogeneity of symptoms seen in clinical practice. 2) The modelled mean starting age (40 years) in the company's base-case is substantially lower than the mean age in PIONEER and the local EAG expert cohort (51 years). 3) Patients who received avapritinib dose escalation were excluded from the analyses, while this may be acceptable for patients with high symptom burden in clinical practice.
What alternative approach has the EAG suggested?	The EAG requested justification for the chosen TSS categories, modelled mean starting age and exclusion of dose-escalation. Additionally, various scenario analyses were requested informing the patient baseline characteristics and analyses based on the full ITT population with and without dose-escalation, and the moderate and severe population including dose-escalation from PIONEER.
What is the expected effect on the CE estimates?	Company scenario analyses adjusting the mean starting age and including the full ITT population had a minor impact on the ICER. Company scenario analyses on dose escalation did not include additional costs of higher doses, an adjusting for this in the EAG base-case resulted in a substantial increase of the ICER.
What additional evidence or analyses might help to resolve this Key Issue?	An overview of patient characteristics of the moderate to severe subgroups with and without dose-escalation in PIONEER and scenario analyses in which these are used to inform patient characteristics in the economic model.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; TSS = total symptom score; UK = United Kingdom	

Table 1.9: Key Issue 8: Questionable generalisability of the SDT basket to UK clinical practice

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	The EAG is concerned that the modelled SDT basket is not reflective of UK clinical practice based on the inclusion of off-label TKIs and concerns of the EAG's clinical expert related to the types of treatments included and the proportions of patients receiving these.
What alternative approach has the EAG suggested?	The EAG requested justification for the inclusion of off-label TKI's and why these were not included for patients on avapritinib + SDT.
What is the expected effect on the CE estimates?	Exclusion of off-label TKIs from the SDT basket substantially increases the ICER.
What additional evidence or analyses might help to resolve this Key Issue?	Scenario analyses including a SDT basket that is reflective of the EAG's clinical expert inputs.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; SDT = symptom-directed therapy; TKI = tyrosine kinase inhibitor; UK = United Kingdom	

Table 1.10: Key Issue 9: Likely under-estimation of avapritinib treatment duration and potential inappropriateness of 24-week stopping rule

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Three discrete treatment discontinuation events (due to AEs, a 24-week stopping rule, and long-term) are modelled that result in significant discrepancies between modelled and observed number of patients on avapritinib treatment over time. The stopping rule at 24 weeks is likely inappropriate as not in line with the evidence or the SmPC.
What alternative approach has the EAG suggested?	Survival analysis on PIONEER time to treatment discontinuation events (see Figure 1 in clarification response).
What is the expected effect on the CE estimates?	Unclear because the three discontinuation events can only be addressed individually in the current model and it is unclear whether the scenario disabling the 24-week stopping rule is implemented correctly as there is a mis-match between trial and model health state distribution at 24 weeks even when the response assessment is disabled. Currently, this scenario results in higher avapritinib costs and QALYs, resulting in an increased ICER.
What additional evidence or analyses might help to resolve this Key Issue?	Survival analysis on PIONEER time to treatment discontinuation events (see Figure 1 in clarification response).
AEs = adverse events; CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SmPC = Summary of Product Characteristics	

Table 1.11: Key Issue 10: Potential disease progression is not fully reflected in the model, SDT long-term effectiveness assumed to be equal to baseline

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Given the short trial duration for the SDT arm, and the observed effect until the end of the trial, there is uncertainty about disease progression and the company's assumption that patients revert back to baseline after the observed follow-up period. Given that for avapritinib the last health state occupation is carried forward after the end of the trial, the assumption may inflate the treatment effect. Small patient numbers at the end of follow-up may result in unstable health state distributions.
What alternative approach has the EAG suggested?	Patients in the SDT arm stay in their last observed health state unless they progress to smouldering or advanced SM. The minimum number of patients needed for calculating health state distributions is set to 20.
What is the expected effect on the CE estimates?	With both EAG's proposed changes, the ICER increases slightly. But there is uncertainty about the appropriate modelling approach for disease progression.
What additional evidence or analyses might help to resolve this Key Issue?	Explore evidence for the natural history of the disease.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; SDT = symptom-directed therapy; SM = systemic mastocytosis	

Table 1.12: Key Issue 11: Progression to SSM and AdvSM is unequal in both arms, inducing a mortality benefit for patients on avapritinib

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Progression to SSM and AdvSM is unequal in both arms, inducing a mortality benefit for patients on avapritinib. This is partly caused by stratification of progression rates by ISM health states, which is not evidence-based, and partly by multiple errors in the modelling, which result in these progressions being inadequately captured.
What alternative approach has the EAG suggested?	Multiple errors need to be corrected. Then set progression probabilities equal across starting health states.
What is the expected effect on the CE estimates?	The EAG's exclusion of SSM and AdvSM decreases the ICER, but since the company's ICERs are incorrect, it is unclear what would happen if the preferred EAG solution (progression probabilities independent of ISM health state) were correctly implemented.
What additional evidence or analyses might help to resolve this Key Issue?	As above.
AdvSM = advanced systemic mastocytosis; CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ISM = indolent systemic mastocytosis; SSM = smouldering systemic mastocytosis	

Table 1.13: Key Issue 12: Utility benefit for avapritinib responders

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	A utility benefit is applied to avapritinib responders ($\geq 30\%$ reduction in TSS) who experience clinically meaningful symptom improvement but remain in the severe health state, even though the utility estimate for the severe health state was derived from a mix of responders and non-responders; the EAG is concerned that this may introduce double-counting.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis removing the additional utility benefit for severe avapritinib responders.
What is the expected effect on the CE estimates?	The exclusion of utility benefit for severe avapritinib responders decreased the incremental QALYs and increased the ICER slightly.
What additional evidence or analyses might help to resolve this Key Issue?	Provide evidence for utility values that were measured with both responders and non-responders do not capture symptom improvements appropriately.
CE = cost effectiveness; EAG = External Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; TSS = total symptom score	

Table 1.14: Key Issue 13: Approach for the estimation of the ISM health state utilities

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	No explicit imputation of missing EQ-5D or TSS data from PIONEER was applied in the base-case. Analyses were conducted using observed data only. Cross-sectional ordinary LS regression was used to estimate

Report Section	4.2.8
	health state-specific utility values, with EQ-5D utilities regressed on TSS severity categories.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis using imputed data from the PIONEER trial. The company used the LOCF methodology for missing EQ-5D utility observations, but the EAG considers this approach inadequate and recommends implementing MMRM or MI in the base-case.
What is the expected effect on the CE estimates?	The LOCF scenario analyses increased the incremental QALYs by [REDACTED] and decreased the deterministic base-base ICER by [REDACTED] but no information is available on the impact of the requested analyses.
What additional evidence or analyses might help to resolve this Key Issue?	Results of a fully imputed model (i.e., MMRM or MI) informing ISM health state utilities. This should explore covariates including (but not limited to) treatment arm and disease severity, and include a binary response covariate to statistically test whether avapritinib response utility improvement is appropriate.
CE = cost effectiveness; EAG = External Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ISM = indolent systemic mastocytosis; LOCF = Last Observation Carried Forward; LS = least squares; MI = Multiple Imputation; MMRM = Mixed Models for Repeated Measures; QALY = quality adjusted life year; TSS = total symptom score	

Table 1.15: Key Issue 14: Resource use benefit for avapritinib responders

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The company consulted a Dutch advisory board for the frequency and nature of health state unit costs, but the values could not be verified, and they were provided for responders and non-responders only and not stratified by health state. In the model, the responder benefit appears to be applied to all patients remaining on avapritinib instead of responders only.
What alternative approach has the EAG suggested?	Clarify the exact source for all values used. Using the information from UK clinical experts on the frequency and nature of health state unit costs. Apply responder benefit to responders only.
What is the expected effect on the CE estimates?	Removing the responder benefit increases the ICER.
What additional evidence or analyses might help to resolve this Key Issue?	Explore whether there is external evidence on real-world resource use data or possibly further clinical expert opinion.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

1.6 Summary of the EAG's view

Table 1.16: Summary of EAG’s preferred assumptions and ICER

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
Deterministic CS base-case									
Avapritinib	██████	██████	██████	█	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_1: Excluding SSM and AdvSM									
Avapritinib	██████	██████	██████	█	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_2: Disable stopping rule after 24-week response assessment									
Avapritinib	██████	██████	██████	█	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_3: Remove utility benefit for responders									
Avapritinib	██████	██████	██████	█	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_4: Align mean starting age with the PIONEER overall ITT/safety population and EAG clinical expert estimate									
Avapritinib	██████	██████	██████	█	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_5: Exclude off-label TKIs from SDT basket									

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_6: Use a minimum of data available for 20 patients instead of for 10 patients to calculate health state distribution									
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_7: After trial end, SDT patients remain in their last observed health state									
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG base-case									
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_8 Scenario: Include dose escalation population and costs of escalated cost with correction to the calculation									
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_9 Scenario: Remove responder benefit on resource use									
Avapritinib	██████	██████	██████	██████	██████	██████	██████	██████	██████
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; LYs = life-years; NHB = net health benefit; QALY = quality-adjusted life-year; SDT = symptom-directed therapy; SSM = smoldering systemic mastocytosis; TKI = tyrosine kinase inhibitor; WTP = willingness-to-pay									

Table 1.17: Probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
Probabilistic CS base-case							
Avapritinib	██████	██████	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████
Probabilistic EAG base-case							
Avapritinib	██████	██████	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████
EAG_8 Scenario: Include dose escalation population and costs of escalated cost with correction to the calculation							
Avapritinib	██████	██████	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████
EAG_9 Scenario: Remove responder benefit on resource use							
Avapritinib	██████	██████	█	█	█	█	█
SDT	██████	██████	██████	██████	██████	██████	██████
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life-year; SDT = symptom-directed therapy; WTP = willingness-to-pay Severity modifier of 1.0 is used for all analyses							

2. Critique of company's definition of decision problem (DP)

Table 2.1: Statement of the DP (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	Adults with inadequately controlled moderate to severe ISM.	Adults with inadequately controlled moderate to severe ISM as per marketing authorisation and PIONEER trial population.	Not applicable.	The population in the DP appears to be narrower than that in the scope, but it is ambiguous given reference to the marketing authorisation and the trial, and potential issues related to the definition of inadequately controlled and moderate to severe.
Intervention	Avapritinib as an add-on to standard care.	Avapritinib (Ayvakyt®) as an add-on to SDT (also termed BSC in clinical practice and PIONEER trial).	SDT terminology aligns more accurately with UK and international clinical practice reflecting the lack of specific therapies for patients with ISM.	There is ambiguity as to the treatments that avapritinib is to be added given use of multiple terminology and the availability of multiple types of treatment in clinical practice. There is also uncertainty in dosing in that dose escalation was permitted in the trial, but it would be outside of the marketing authorisation.
Comparator(s)	ECM without avapritinib.	SDT as the ECM without avapritinib. Note should be made that no therapeutic agents are currently approved/reimbursed specifically for ISM in England/ Wales. Current SDT is directed	SDT terminology aligns more accurately with UK and international clinical practice reflecting the lack of specific therapies for patients with ISM.	As stated above, there is ambiguity as to the treatments that avapritinib is to be added to, which also applies to those treatments as comparators.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
		solely at alleviating symptom burden.		
Outcomes	The outcome measures to be considered include: • symptom severity • mast cell burden • response rate • adverse effects of treatment • HRQoL • mortality	The outcome measures to be considered include: • symptom severity • mast cell burden • response rate • adverse effects of treatment • HRQoL • mortality (included as a SAE).	The outcome measures to be included in the CS are in line with the final scope. Due to the pathogenesis of ISM, mortality is not a key outcome captured in the PIONEER clinical trial, except as part of the safety profile hence the minor amendment.	The outcomes in the DP match those in the scope.
Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and CE 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	In line with NICE final scope, however, PAS is not confirmed but this is expected to follow a previously agreed discount used in TA1012.	Not applicable.	Consistent with the NICE reference case.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	No subgroups specified, submission to focus on marketing authorisation.	Blueprint Medicines would like to clarify that this submission covers the full marketing authorisation of avapritinib for the treatment of adult patients with moderate to severe symptoms of ISM inadequately controlled by symptomatic treatment.	Not applicable.	No comment.
Special considerations including issues related to equity or equality	No issues relating to equity or equality raised in the scope.	Blueprint Medicines do 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 gelatin as an excipient. Inclusion of gelatin 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 gelatin-free treatment option is important to ensure access for all patients regardless of religious or cultural beliefs.	Not applicable.	No comment.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Based on Table 1 of the CS¹ BSC = best supportive care; CE = cost effectiveness; CS = company submission; DP = decision problem; EAG = External Assessment Group; ECM = established clinical management; HRQoL = health-related quality of life; ISM = indolent systemic mastocytosis; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; PSS = Personal Social Services; QALY = quality-adjusted life year; SAE = serious adverse event; SDT = symptom-directed therapy; TA = Technology Assessment; UK = United Kingdom				

2.1 Population

The population in the National Institute for Health and Care Excellence (NICE) scope is: Adults with inadequately controlled moderate to severe indolent systemic mastocytosis (ISM).² The population in the decision problem (DP) is adults with inadequately controlled moderate to severe ISM as per marketing authorisation and PIONEER trial population.¹

EAG comment: The company were asked to describe precisely how the marketing authorisation and the PIONEER trial define the population, noting any differences between the marketing authorisation and the trial, and to clarify that the former will determine the eligible population in English clinical practice. Specifically, the following are eligibility criteria in PIONEER:

- As per the established World Health Organization (WHO) criteria, patients exhibiting <2 B-findings and no C-findings are diagnosed with ISM. This was confirmed to be the method used in United Kingdom (UK) clinical practice by one of the External Assessment Group (EAG) clinical experts (SM).³
- Moderate to severe symptoms based on a minimum mean total symptom score (TSS) of ≥ 28 on the ISM-Symptom Assessment Form (ISM-SAF) over a 14-day eligibility screening period. One of the EAG clinical experts (SM) stated:³ *“Currently the ISM-SAF is not used in all centres – although it is being increasingly adopted. Some centres may currently use other criteria”*. The other one (SW) stated:⁴ *“TSS is not often carried out outside of the research setting and was primarily developed for research. Patient's interpretation of how to fill this out will vary, and it is a useful measure to see how the patient's symptoms are changing, but may be less useful when comparing symptoms between patients. The mastocytosis quality of life questionnaire focuses more on the impact of symptoms on patient's life rather than symptoms severity, and may be a better way to assess impact in clinic.”*

The company responded that:⁵ *“NHS clinical practice is expected to follow the marketing authorisation for avapritinib in patients, as confirmed by clinical experts, which is based on the PIONEER pivotal trial.”* They also stated: *“Only patients with a confirmed ISM diagnosis (according to WHO 2022 systemic mastocytosis criteria; see CS Section 1.3.3) will be eligible for avapritinib in UK clinical practice in England.”* In terms of severity they stated: *“As the marketing authorisation does not specify ISM-SAF (or the threshold score of ≥ 28 TSS), this is not required implicitly as criteria for moderate to severe patients with ISM. This tool does and will not dictate clinical practice but qualitatively informs management of patients alongside expert judgement and more quantitative measures.”* This seems to align with the EAG clinical expert, which suggests that there might be some discrepancy between PIONEER and UK clinical practice. In relation to the effect of any discrepancy, the company stated: *“Clinical and cost-effectiveness are based on PIONEER clinical trial data and ISM-SAF derived health states (mild, moderate, and severe). NHS clinical practice in England and Europe is aligned with the eligibility criteria of the PIONEER pivotal trial which is currently conducted in 3 sites in the UK (as part of the OLE phase). Clinical practice in the UK is informed by clinician judgement and expertise informed by objective measures of mast cell burden as well as patient-reported outcome measures (including ISM-SAF, the specifically designed tool for patients with ISM). As such there is alignment between diagnostic criteria used in the PIONEER trial and NHS clinical practice, hence no discernible implication on clinical or cost-effectiveness.”*

In conclusion, it appears that in UK clinical practice patients will be chosen mostly according to the WHO criteria, which aligns with PIONEER. However, it appears that the ISM-SAF might not be used, which does not align with PIONEER, which creates some uncertainty as to how patients would be regarded as having moderate to severe symptoms for avapritinib. It should also be noted that company elicited clinical expert suggested that severity judged by the ISM-SAF is also not sufficient to determine

who might benefit from avapritinib. One stated:⁶ “...the clinical experts noted that some patients with severe skin disease but low symptom scores could fall outside this definition. For example, if ISM patients: 1. Their total symptom scores may not reach threshold despite profound quality-of-life impairment. OR 2. These patients may be managed with PUVA and antihistamines but could still benefit substantially from avapritinib.” The implications are difficult to predict, although the main risk seems to be that those with mild symptoms according to the ISM-SAF might be considered for avapritinib. In fact, the company clinical experts were asked:⁶ “In your clinical practice, would you likely treat patients with mild ISM with avapritinib?”, to which the response was generally no, although one stated: “Possible if one severe symptom meaningfully impairs daily QoL and there is involvement of a second organ system (e.g., severe diarrhoea + another system).” Therefore, it seems that some patients outside of the PIONEER population because they have mild disease according to the ISM-SAF might be considered for avapritinib in clinical practice if the disease affecting only one system e.g. the skin, is regarded as severe. This is therefore highlighted as a Key Issue.

2.2 Intervention

The intervention is avapritinib as an add-on to standard care in the NICE scope.² It is described as an add-on to symptomatic-directed therapy (SDT), also termed best supportive care (BSC) in the DP and the PIONEER trial.¹ Figure 11 in the company submission (CS) shows that avapritinib is accompanied by BSC.

EAG comment: Given the use of various terminology for the treatment to which avapritinib is to be added, and the variation in treatments that are available in clinical practice, the EAG sought some clarification as to how avapritinib would be used in UK clinical practice. One of the EAG clinical experts stated that avapritinib would be added to SDT:³ “...if symptoms not adequately controlled”, which does seem to be consistent with the DP.

The company responded:⁵ “Avapritinib is administered as an add-on to SDT, and not by itself, to target the underlying KIT D816V pathophysiology of ISM rather than just alleviating symptoms.” This would seem to clarify the way that avapritinib would be used in clinical practice, although it should be noted that in the economic model some tyrosine kinase inhibitor (TKI) use was assumed for the comparator and none for the avapritinib cohort, although TKIs might not be considered as SDT: this is discussed further in Section 2.3.

It should also be noted that the marketing authorisation for avapritinib is the 25 mg dose, and this was used in the economic model.¹ However, dose escalation was permitted in PIONEER part 3, and one of the EAG clinical experts stated:⁴ “There was a ■■■ grade 3 reaction rate with 50mg, rising to ■■■ with 100mg (esp nausea, headache, diarrhoea). These are similar symptoms to those of ISM anyway, and patients may therefore find this an acceptable risk. For patients with very high symptom burden this would therefore be an acceptable risk, and the dose remains much lower than doses used for SM. It may therefore have been more helpful if the patients with dose escalation hadn’t been excluded.” This does therefore raise a question as to whether dose escalation would occur in clinical practice, and consequently the generalisability of the trial data and the applicability of the economic model to UK clinical practice. This is therefore a Key Issue.

2.3 Comparators

The comparator is described as established clinical management (ECM) without avapritinib in the NICE scope, and SDT in the DP.^{1, 2} Figure 11 lists the following treatments in the final branch of the therapeutic pathway: interferon-alpha, omalizumab, cladribine, TKIs and BSC.

EAG comment: It is noteworthy that NICE also seem to use terms interchangeably i.e. ECM for the comparator even though the intervention is added to ‘standard care’. As for the intervention, the EAG sought clarification as to the precise nature of current UK clinical practice: The EAG used the term ‘treatments for patients who would be eligible of avapritinib’ in order to avoid using any of the more ambiguous terms i.e. ECM, standard care or BSC. One of the EAG clinical experts stated that ECM and SDT are not:³ “*completely synonymous*”, and that SDT would refer to antihistamines, antileukotrienes, mast cell stabilisers, and H1/2 antagonists.⁷ She stated that ECM would also include treatment not for symptom control e.g. for osteoporosis treatment/prevention, such as vitamin D or bisphosphonates. Finally, she stated that interferon-alpha, cladribine, and TKIs:³ “*would be regarded as disease modifying – aimed at decreasing the mast cell burden not just controlling symptoms These are mainly indicated for AdvSM*”. This last statement does therefore cast doubt on the inclusion of such disease modifying treatments. The other EAG clinical expert (SW), provided percentage use of each of the treatments that would be used in UK clinical practice in response to questions about how treatments were modelled (see Section 4.2.4.), which indicated no use of interferon-alpha, cladribine, or TKIs.⁴

The company responded:⁵ “*Established clinical management is equivalent to symptomatic-directed therapy (SDT) as noted throughout the submission. In published studies of patients with ISM (Gotlib et al. [2023]), best supportive care (BSC) is the terminology used to describe this ‘standard care’ basket. This submission has aligned BSC to SDT to better reflect the nature of these symptomatic therapies and individual patient needs according to heterogeneous and evolving symptomatology. SDT, unlike avapritinib, does not tackle the underlying pathophysiology of ISM.*” They stated: “*Clinical experts confirmed that cladribine and interferon were not considered part of the SDT management in clinical practice, hence their exclusion from the economic model.*” However, they also stated: “*Patients with moderate to severe ISM are currently managed in UK clinical practice with symptomatic treatments including H1-/H2-blockers (antihistamines), proton-pump inhibitors (PPI), leukotriene inhibitors, corticosteroids, mast cell stabilisers, anti-diarrhoea medication, and off-label omalizumab (monoclonal antibody). Avapritinib would be administered alongside these SDT options, it is not intended to replace symptomatic treatments.*” This indicates that omalizumab would be included as SDT, but according to Figure 11 in the CS, as stated above, it is not regarded as BSC, which the company contradicts the alignment of BSC with SDT. The EAG clinical experts (SM and SW), responded that omalizumab would be used for <5% and 5% of patients respectively. SM also stated that it would be used only for those patients: “*with recurrent anaphylaxis or severe urticaria*”, and SW stated that it would not be used in addition to avapritinib, which implies that avapritinib would replace it.

In conclusion, the EAG clinical experts seem to agree on some aspects of what clinical practice is, that this largely can be regarded as SDT, and that interferon alfa and cladribine can be excluded. Although omalizumab was not counted as BSC by the company and BSC was stated to be equivalent to SDT, it was included in the economic model and by the EAG clinical experts. Therefore, it seems reasonable to also include it as part of SDT. However, although the company and EAG clinical experts seem to agree that TKIs are not part of SDT, the company have added them as part of the comparator in the economic model. They also assume zero percent use for the intervention i.e. that avapritinib would replace them. There are also differences between the company percentage use of treatments in the model

and the EAG clinical expert (SW), further details of which are presented and discussed in Section 4. Therefore, what should be considered as SDT or ECM is regarded as a Key Issue.

2.4 Outcomes

The outcomes in the scope and DP are essentially the same.^{1, 2}

EAG comment: No further comment.

2.5 Other relevant factors

None.

EAG comment: No comment.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.⁸ The evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) from Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) was used to inform this critique.⁹

Appendix B of the CS¹⁰ details the systematic literature review (SLR) conducted to identify relevant clinical evidence for the use of avapritinib for treating inadequately controlled moderate to severe ISM. Searches were conducted on 28 July 2025.

EAG comment:

- The CS¹ and Appendix B,¹⁰ provided sufficient details for the EAG to appraise the literature searches.
- The clinical effectiveness search was well constructed, including subject headings. A good range of synonyms were used, particularly in the intervention facet. The search was well documented and is reproducible.
- A good range of databases were searched from inception on 28 July 2025: MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations), Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials.
- No date or language limits were applied to the Embase, MEDLINE or Cochrane Library searches, and no publication type, study design filters or human limits were applied to the Embase or MEDLINE searches.
- Twenty-two conference proceedings were searched manually, where available, for the years 2023-2025. Eleven Health Technology Assessment (HTA) websites were searched, and two clinical trials registries, for that same date range. The EAG query whether earlier years could also have been searched for the HTA material. The EAG could not see the date on which these grey literature searches were undertaken. It was not clear to the EAG which of the available date options were used in ClinicalTrials.gov to limit the timespan.
- The EAG feel that for the grey literature searches, the number of hits before screening should be the figure reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in Figure 1 in Appendix B¹⁰, to match how the numbers of results from the database searches were reported. The PRISMA flowchart records that reference checking was undertaken, but there are no details of this in Appendix B.¹⁰

3.1.2 Inclusion criteria

Table 3.1 details the eligibility criteria that was employed in the company SLR to identify relevant evidence.¹ As already described in Section 2.3 of this report, the EAG were concerned with how comparator treatments were defined and had requested some clear guidance on this. Briefly our concern was that comparator is described as ECM without avapritinib in the NICE scope, and SDT in the DP. Additionally, the comparator listed on Table 3.1 for the evidence eligibility criteria lists 'best supportive care' and emphasises that this is 'author defined'. These are of course ambiguous definitions and the company stated '*...best supportive care (BSC) is the terminology used to describe this 'standard care' basket. This submission has aligned BSC to SDT to better reflect the nature of these symptomatic therapies and individual patient needs according to heterogeneous and evolving symptomatology*'⁵. The EAG sought clinical advice on what would likely be suitable comparator treatments according to the

various definitions (addressed in Section 2.3) and were advised that these definitions (ECM and SDT) are not synonymous. Given that there is uncertainty over such definitions and what would therefore constitute relevant and appropriate comparator treatments, it is feasible that the eligibility criteria and screening process may not have identified relevant studies through error, definition misalignment, or uncertainty.

Table 3.1: Eligibility criteria used in search strategy for clinical evidence

	Inclusion	Exclusion
Population	Adult (age ≥ 18 years) patients with non-AdvSM^a which includes: • ISM • SSM	Any other population, including, but not limited to: • AdvSM • ASM • MCL • SM with an AHN • Patients with diseases other than non-AdvSM • Paediatric population • Healthy volunteers
Interventions	Avapritinib Immunoglobulin Other TKIs including: • Imatinib • Masitinib • Midostaurin • Bezucastinib • Ripretinib • HT-KIT • Lirontelimab Standard of care including: • H1-antihistamine (e.g., ranitidine, famotidine) • Leukotriene receptor antagonist • PPI • Sodium cromoglycate • Omalizumab Any investigational treatment other than TKIs, including: • Allogeneic stem cell transplantation • Chlorodeoxyadenosine (Cladribine or 2-CdA) • Interferon-alpha	Any treatment not listed in the inclusion criteria

	Inclusion	Exclusion
Comparators	Placebo BSC (author defined) Any other pharmacological/non-pharmacological intervention No comparator limit for single-arm studies	None
Outcomes	Efficacy • Change in serum tryptase levels • Change in KIT D816V VAF • Change in BM MC aggregates • Change in BM MC • Proportion of patients with a $\geq 50\%$ reduction in BM MCs or no aggregates for patients with aggregates at baseline • Change in BSC concomitant medication usage • ORR (including complete and partial remission and their definitions) • DoR • Safety • AEs • SAEs • Study/treatment discontinuation • Discontinuation due to AEs • HRQoL/PRO • Change in ISM -SAF TSS, MC-QoL, MSAF, PGIS, SF-12, PGIC, EQ-5D, MS2D2	Studies that do not report any of the outcomes of interest specified in the inclusion criteria
Study design	RCTs Non-RCTs Single arm studies Retrospective and prospective cohort studies RWE studies SLRs and meta-analysis of RCTs/observational studies ^b	Letters, comments, and editorials Case-series or case reports or case studies Economic studies Pre-clinical studies
Language restrictions	No limits	None
Countries	No limits	None
Time limit	No limits	None

	Inclusion	Exclusion
Source: Adapted from Table 6, Appendix B¹⁰ AEs = adverse events; ASM = aggressive systemic mastocytosis; BM = bone marrow; BSC = best supportive care; CR = complete response; DoR = duration of response; EQ-5D = European Quality of Life-5 Dimensions; EU = European Union; HRQoL = health-related quality of life; ISM = indolent systemic mastocytosis; MC = mast cell; MCL = mast cell leukaemia; MC-QoL = mastocytosis quality of life questionnaire; MSAF = Mastocytosis Symptom Assessment Form; MS2D2 = Mastocytosis Symptom Severity Daily Diary; NICE = National Institute of Health and Care Excellence; non-AdvSM = non-advanced systemic mastocytosis; ORR = overall response rate; PGIC = Patients Global Impression of Change; PGIS = Patient Global Impression of Severity; PPI = proton-pump inhibitor; PR = partial response; PRO = patient-reported outcome; RCTs = randomised controlled trials; RWE = real-world evidence; SAE = serious adverse event; SAF = Symptom Assessment Form; SF-12 = 12-item short form survey; SLR = systematic literature review; SM = systemic mastocytosis; SSM = smouldering systemic mastocytosis; TKIs = tyrosine kinase inhibitor; TSS = total symptom score; VAF = variant allele fraction Notes: ^a Studies assessing mixed population of SM were included at the abstract/title screening stage. At the full text screening stage, studies were only included if data is reported separately for non-AdvSM types: ISM and SSM. Furthermore, for all the studies included during the secondary screening stage, the definitions and criteria used for the disease were captured in the data extraction grid. ^b Bibliographies of SLR articles were screened to ensure that all relevant studies are identified in the SLR.		

3.1.3 Critique of screening and data extraction

The company state in Appendix B of the CS¹ that level 1 screening was performed by two independent NHTA reviewers who reviewed each reference identified in the literature search, applied basic study selection criteria and included or excluded the record. They state that uncertainties regarding the inclusion of studies was checked by a third reviewer.

Full text screening of potentially relevant articles was independently reviewed by two independent reviewers against each eligibility criterion: again, with any uncertainties being decided by a third reviewer.

Data extraction was conducted with a less robust method. According to Appendix B of the CS¹⁰ one reviewer extracted the data from the included full-text articles by completing agreed standard data extraction shells for clinical SLR with all extracted data then quality checked against the original source article by a second reviewer.

EAG comment: The company have described a screening process which appears to be an optimal method for reducing the likelihood of error and bias when determining study inclusion against the eligibility criteria. Screening conducted independently by two separate reviewers, that is then combined with any disagreements decided by a third reviewing as adjudicator was employed for both stages of screening, thereby serving to minimise any errors or biases. Data extraction was only conducted by one reviewer however, with a quality check conducted by a second. This is a method that is often used, and the check by the second reviewer does offer some protections against increased errors or biases, however it is not as robust as the method that was utilised for screening and carries a higher likelihood of errors with increased risk of bias.

3.1.4 Quality assessment

Quality assessments of the relevant evidence were completed using the NICE critical appraisal checklist for randomised controlled trials (RCTs). The publication quality assessment for non-

RCTs/observational studies were completed using the Downs and Black checklist¹⁰. The PIONEER trial was identified from the SLR and included in the submission. The company appraisal of the PIONEER trial is included in the Table below alongside any EAG comments where necessary or appropriate.

Table 3.2: Quality appraisal results

Gotlib (2023) PIONEER (NCT03731260)							
Appraisal item	1	2	3	4	5	6	7
Company appraisal	Yes	Yes	Yes	Yes	No	No	Yes
EAG comment if required	N/A	N/A	Generally, well balanced at phase 2 but some differences (>5%) in characteristics	N/A	N/A	N/A	N/A
Source: Adapted from Table 20, Appendix B, CS ¹⁰ CS = company submission; EAG = Evidence Assessment Group; ITT = intention-to-treat; N/A = not applicable Notes: Appraisal items 1. Was randomisation carried out appropriately? 2. Was the concealment of treatment allocation adequate? 3. Were the groups similar at the outset of the study in terms of prognostic factors? 4. Were the care providers, participants, and outcome assessors blind to treatment allocation? 5. Were there any unexpected imbalances in dropouts between groups? 6. Is there any evidence to suggest that the authors measured more outcomes than they reported? 7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?							

EAG comment: The company in their submission state that the process for conducting appraisals was the same as that for data extraction and therefore utilised one reviewer to conduct the appraisal, with a second reviewer conducting a quality check. This is a common approach and while it does serve to offer some limitations to error or bias, it is not as robust or reliable as a duplicate assessment with disagreements resolved by consensus or the involvement of a third reviewer. The EAG conducted an appraisal of the trial and found no major disagreements with the company appraisal. The EAG notes that participants seem well balanced in general terms at phase 2 of the trial, however some group differences (>5%) do appear to be evident.

3.1.5 Evidence synthesis

There was only one trial, which is PIONEER.

EAG comment: None required.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

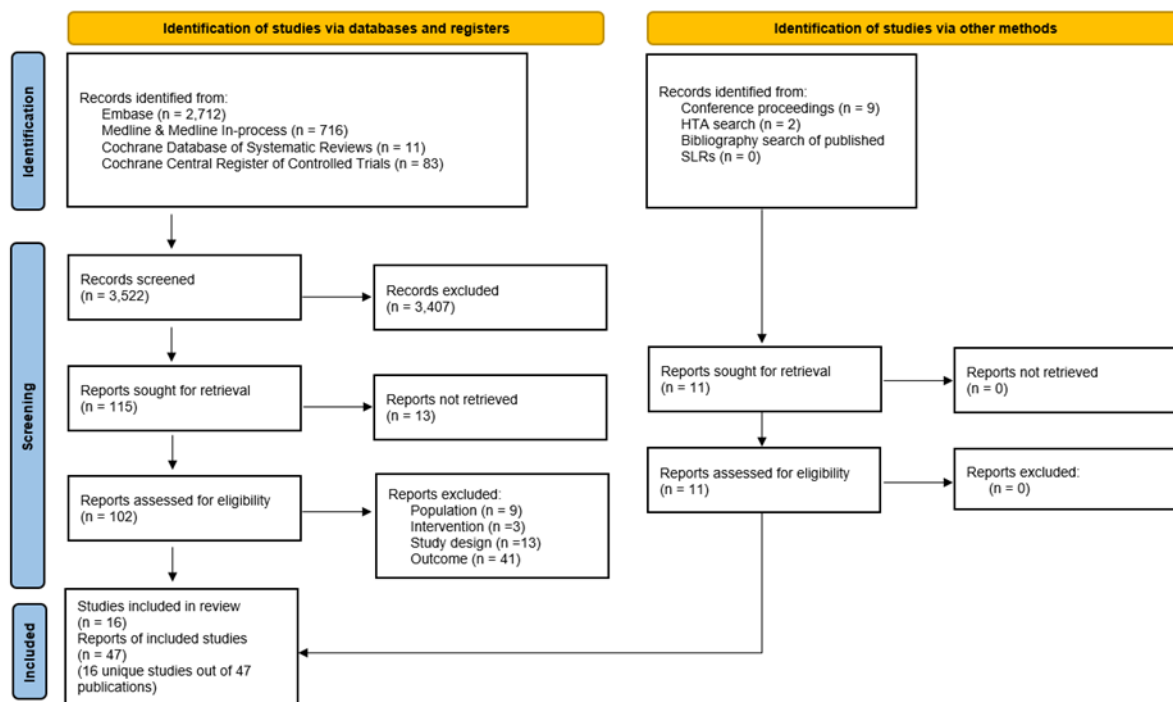
3.2.1 Study retrieval

There were 3,522 publications initially identified and screened from multiple databases (see Figure 3.1). Of these, 3,407 were excluded. Therefore 115 publications underwent further evaluation of eligibility. Thirteen paid articles could not be retrieved, and 66 publications were then excluded.

The grey literature search identified 11 relevant publications and so a total of 47 publications were included in the review. Some studies were associated with multiple publications and so secondary

publications were combined. Hence, four RCTs from 32 publications, three single arm studies from five publications and nine observational studies from 10 publications were deemed relevant.

Figure 3.1: PRISMA flow chart of evidence identification

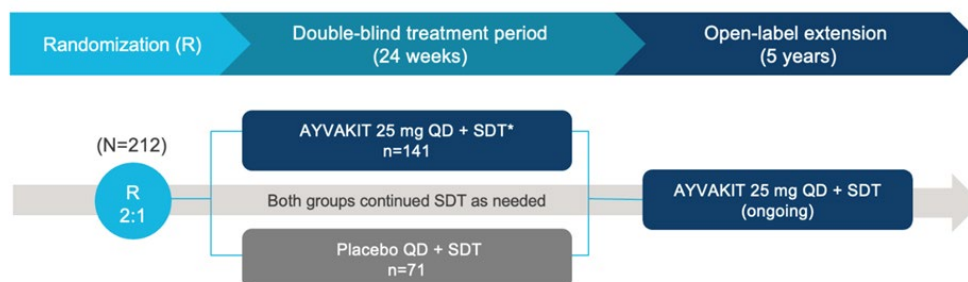


HTA = Health Technology Assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

3.2.2 Summary of details of PIONEER trial

The details of the PIONEER trial are described here as summarised and presented within the CS¹. This was a phase 2, randomised, double-blind, placebo-controlled study, conducted over three parts with the purpose of evaluating avapritinib once daily (QD) in patients with ISM. The study was conducted in a sequential manner with the first part being concerned with dose escalation to determine the recommended efficacious dosage for the second phase. The second part was the pivotal randomised, double-blind, placebo-controlled trial with a 2:1 randomisation ratio (avapritinib 25 mg + SDT to placebo + SDT). The third part was an open label extension (OLE) designed to assess long-term safety and efficacy. Screening was conducted over a period of up to 8 weeks with a 2-week symptom assessment period included. Stratification was implemented based on serum tryptase levels at screening (<20 ng/mL versus ≥20 ng/mL).¹

Figure 3.2: PIONEER Phase 2 trial study design



Source: Adapted from Figure 12, CS¹

CS = company submission; ISM = indolent systemic mastocytosis; OLE = open label extension; QD = once daily; SDT = symptom-directed therapy

Note:

* The recommended dose of avapritinib for the double-blind period and OLE was identified in Part 1 of PIONEER

The inclusion criteria for the study consisted of the following:¹

- Adults aged ≥ 18 years with centrally confirmed WHO diagnosis of ISM
- Moderate to severe symptoms based on minimum mean TSS of ≥ 28 on the ISM-SAF over a 14-day eligibility screening period
- Inadequate symptom control for ≥ 1 baseline symptoms despite optimised therapy with ≥ 2 symptom-directed treatments
- For participants receiving corticosteroids, stable dose of ≤ 20 mg/day prednisone or equivalent for ≥ 14 days prior to screening
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2

Key exclusion criteria for the PIONEER trial included¹:

- Diagnosis of other WHO SM subclassifications (cutaneous mastocytosis, SSM, SM with associated haematological neoplasm, aggressive SM, mast cell leukaemia [MCL] or mast cell sarcoma)
- Prior treatment with avapritinib
- Recent cytoreductive therapy (< 14 days or 5 half-lives, whichever longer)
- Recent radiotherapy or psoralen ultraviolet A therapy (< 14 days)
- Haematopoietic growth factor use within 14 days before eligibility assessment
- QT interval corrected using Fridericia's formula (QTcF) > 480 msec

The primary endpoints across the PIONEER study included¹

- Part 1: Determination of the recommended Phase 2 dose (RP2D) of avapritinib
- Part 2: Mean change in ISM-SAF TSS from baseline to week 24
- Part 3: Change from baseline in ISM-SAF TSS through up to 3 years, including proportions with $\geq 30\%$ and $\geq 50\%$ reductions

Key secondary endpoints for Part 2 included¹:

- Proportion of participants with $\geq 50\%$ reduction in serum tryptase from baseline to week 24
- Proportion of participants with $\geq 50\%$ reduction in peripheral blood KIT D816V VAF or undetectable ($< 0.02\%$) at week 24
- Proportion of participants achieving $\geq 50\%$ reduction in ISM-SAF TSS at week 24
- Proportion of participants achieving $\geq 30\%$ reduction in ISM-SAF TSS at week 24
- Proportion of participants with $\geq 50\%$ reduction in bone marrow (BM) mast cells (MCs) or elimination of known baseline mast cell aggregates at week 24

Additional secondary endpoints for Part 2/3, assessed up to 3 years, included:¹

- Change from baseline in serum tryptase levels
- Change from baseline in KIT D816V VAF
- Additional secondary endpoints included changes in QoL measures (Mastocytosis Quality of Life questionnaire [MC-QoL]; 12-item Short Form Survey [SF-12]; Patient Global Impression of Severity [PGIS]; Patient Global Impression of Change [PGIC]; EuroQoL 5-Dimension 5-Level questionnaire [EQ-5D-5L]), changes in SDT medication usage, changes in domain-specific symptom scores, and safety parameters.

The company emphasise that the original protocol, dated 15 February 2018, was amended 10 times¹ with the latest amendment dated 7 June 2022. The study methodology presented in the CS is in accordance with this amendment. The key modifications included establishing the eligibility threshold of symptom severity (ISM-SAF TSS) ≥ 28 over the 14-day screening period and setting the recommended Phase 2 dose as 25 mg once daily based on Part 1 findings.¹ A clinically important response was defined as $\geq 30\%$ reduction in TSS from baseline. Additional changes were made with the primary endpoint for Part 2 changed from percentage based to mean change in ISM-SAF TSS from baseline to week 24 compared to placebo.¹ Secondary endpoints were expanded to include both moderate ($\geq 30\%$ reduction in ISM-SAF TSS) and substantial ($\geq 50\%$ reduction in ISM-SAF TSS) symptom improvements and objective measures of disease burden ($\geq 50\%$ reduction in serum tryptase and $\geq 50\%$ reduction in KIT D816V VAF).¹

The CS confirms that the study population in Part 2 was refined to focus on people with ISM only, and the statistical analysis method was updated to analysis of covariance accounting for randomisation stratification factors.¹ Further amendments dated 20 July 2023 established post-treatment cessation follow-up procedures, enabling long-term monitoring of objective disease measures and patient outcomes for up to 2 years after treatment discontinuation through regular telephone assessments and optional central laboratory review of local samples.¹

The CS justifies such amendments as being to refine the study design and endpoints based on evolving clinical evidence and regulatory guidance, while maintaining study integrity.¹

An overview of the PIONEER trial is provided in the Table below.

Table 3.3: Overview of PIONEER Phase 2 study methodology

Trial number (acronym)	NCT03731260 (PIONEER)
Trial design	Multicentre, three-part Phase 2 study: [Part 1] Dose escalation [Part 2] Pivotal, double-blind, placebo-controlled RCT [Part 3] Long-term OLE
Eligibility criteria for participants (Key Inclusion)	Adult male and female participants Centrally confirmed WHO diagnosis of ISM Moderate to severe symptoms according to a minimum mean ISM-SAF TSS of ≥ 28 over a 14-day screening period <i>KIT D816V</i> mutation positive
Eligibility criteria for participants (Key Exclusion)	A diagnosis of mastocytosis other than ISM Prior treatment with avapritinib and/or antineoplastic therapy within 28 days or TKI therapy within 14 days before the TSS eligibility assessment
Settings and locations where the data were collected	42 sites, majority located in Europe (n=23), with 19 located in North America
Trial drugs Intervention(s) (n=[x]) and comparator(s) (n=[x])	Part 1: Intervention: avapritinib orally once daily at one of 3 dose levels: 25 mg (n=10), 50 mg (n=10), or 100 mg (n=10) Comparator: placebo + SDT (n=9) Part 2: Intervention: avapritinib 25 mg orally QD + SDT (n=141) Comparator: placebo + SDT (n=71)

Trial number (acronym)	NCT03731260 (PIONEER)
	Based on Part 1 results, 25 mg avapritinib was selected as the RP2D Part 3: Intervention: avapritinib 25 mg daily Dose escalation to 50 mg avapritinib was permitted based on prespecified clinical criteria
Permitted and disallowed concomitant medication	Participants received SDT according to treating physician's discretion All participants were treated with at least 2 current or prior SDT medications (per inclusion criteria) Most common SDTs: antihistamines for systemic use (97.2% in avapritinib group, 100% in placebo group) and drugs for peptic ulcer and gastro-oesophageal reflux disease (73.8% in avapritinib group, 78.9% in placebo group)
Primary endpoints (including scoring methods and timings of assessments)	Part 1: the RP2D in participants with ISM (12 weeks of treatment) Part 2: mean change in TSS of the ISM-SAF from baseline to week 24 Part 3: the long-term safety and efficacy of avapritinib (5 years)
Other endpoints used in the economic model/specified in the scope	≥30% and ≥50% reduction in TSS from baseline at week 24 EQ-5D utility values by disease severity category derived from PIONEER trial and PRISM study Health state distribution by TSS severity categories during initial treatment period (6 cycles) and maintenance phase TRAE incidence rates Patient distribution across mild (TSS 0-27), moderate (TSS 28-41), and severe (TSS 42-110) health states
Further secondary and exploratory endpoints	Change in measures of mast cell burden Change in SDT usage Change in gastrointestinal and skin domains, neurocognitive symptom cluster, and individual symptom scores of ISM-SAF Change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score of ISM-SAF Safety and tolerability (AEs, vital signs, ECGs, lab tests) Pharmacokinetics and correlations between exposure and endpoints Changes in QoL measures (MC-QoL, SF-12, PGIS, PGIC; EQ-5D-5L)
Pre-planned subgroups	Baseline serum tryptase levels (<20 ng/mL versus ≥20 ng/mL) Gender (male/female) Age group (<65/≥65 years) Region (North America/Europe) Baseline ISM severity (moderate/severe) ECOG PS Prior TKI therapy
Duration of follow-up / loss to follow-up / cross-over	Part 2: 24 weeks (6 cycles) of treatment Part 3: OLE up to 5 years (ongoing) Cross-over: after Part 2, participants from both avapritinib and placebo groups could continue/switch to 25 mg avapritinib QD in Part 3 Loss to follow-up in Part 2: 5 participants discontinued from each treatment group (avapritinib or placebo)

Trial number (acronym)	NCT03731260 (PIONEER)
	By Part 3 (DCO 21 February 2025): ■ participants discontinued, ■ participants ongoing in Part 3 ■
Source: Adapted from Table 8, CS ¹ AEs = adverse events; CS = company submission; DCO = data cut-off; ECGs = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQoL 5-Dimension 5-Level questionnaire; ISM = indolent systemic mastocytosis; MC-QoL = Mastocytosis Quality of Life questionnaire; OLE = open label extension; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; QD = once daily; QoL = quality of life; RCT = randomised controlled trial; RP2D = recommended Phase 2 dose; SAF = Symptom Assessment Form; SDT = symptom-directed therapy; SF-12 = 12-item Short Form Health Survey; TKI = tyrosine kinase inhibitor; TRAE = treatment-related adverse events; TSS = total symptom score; WHO = World Health Organization	

3.2.3 Statistical analysis of PIONEER trial

This Section contains an overview and insight of the statistical methods adopted in the PIONEER trial as described and summarised in the CS.¹ PIONEER evaluated six distinct analysis populations, namely (1) intention-to-treat (ITT), (2) per-protocol, (3) safety, (4) dose escalation, (5) long-term and (6) overall. The overall analysis population included participants who received avapritinib at any point, with analyses using the avapritinib baseline.¹ The primary analysis of Part 1 focused on determining the recommended dose for phase 2 based on mean change in ISM-SAF TSS at week 12, comparing each avapritinib dose group (25 mg, 50 mg, 100 mg QD) to placebo. The 25 mg QD dose was ultimately selected based on comparable efficacy to higher doses with improved tolerability.¹ For Part 2, participants with high-dose steroid use in the 7 days before week 24 or for more than 14 days consecutively from week 0 to week 24 were excluded to prevent confounding.¹ A one-sided p-value of <0.025 was required to demonstrate the superiority of the avapritinib + SDT arm in reducing symptoms versus placebo + SDT. The primary efficacy analysis was conducted in the ITT population. The PP population was used for sensitivity analyses.¹ For Part 3, which included participants who rolled over from both Part 1 and Part 2 of the study, long-term safety and efficacy of avapritinib was evaluated using descriptive statistics.¹

Table 3.4: Overview of statistical analysis in PIONEER Phase 2

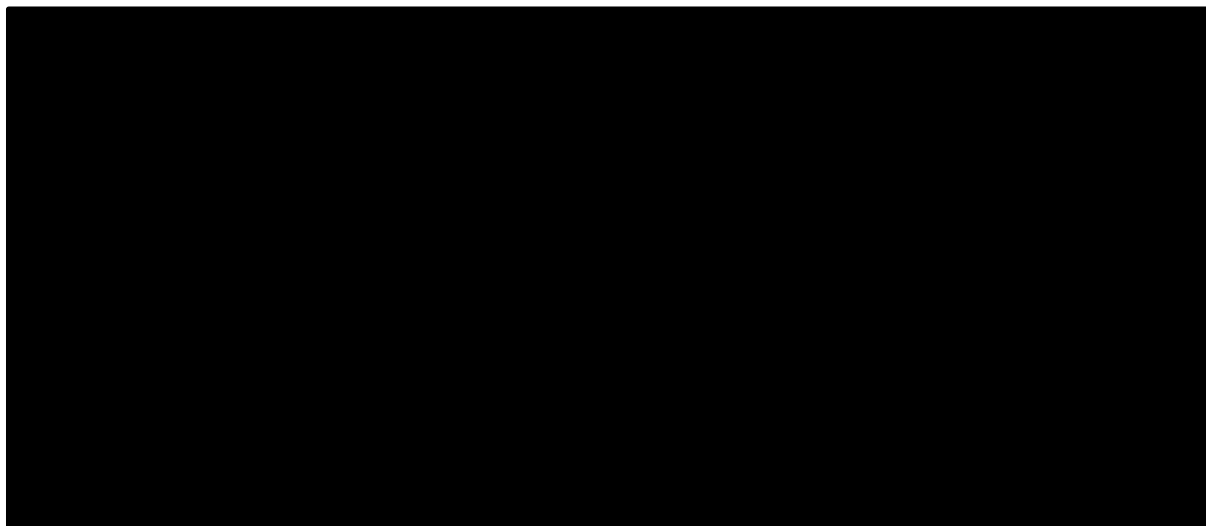
Trial number (acronym)	NCT03731260 (PIONEER)
Study hypotheses	Primary hypothesis: avapritinib 25 mg + SDT QD is superior to placebo + SDT in reducing ISM symptoms as measured by mean change in ISM-SAF TSS from baseline to week 24. Secondary hypotheses: avapritinib + SDT is superior to placebo + SDT in reducing mast cell burden (serum tryptase, <i>KIT D816V</i> VAF, BM MCs) and achieving clinically meaningful symptom reductions ($\geq 30\%$ and $\geq 50\%$ in TSS).
Analysis sets	ITT population: All randomised participants (primary efficacy analyses). Part 1: n=39 (25 mg: n=■; 50 mg: n=■; 100 mg: n=■; placebo: n=■) Part 2: n=212 (25 mg: n=141; placebo: n=71) PP population: ITT participants without major protocol deviations (sensitivity analyses). Part 2: n=190 (25 mg: n=123; placebo: n=67) Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■) Safety population: All participants who received ≥ 1 dose of study drug (safety analyses).

Trial number (acronym)	NCT03731260 (PIONEER)
	Part 1: n=39 (25 mg: n=■; 50 mg: n=■; 100 mg: n=■; placebo: n=■) Part 2: n=212 (25 mg: n=141; placebo: n=71) Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■) Dose escalation population: Participants who underwent protocol-defined dose escalation to 50 mg in Part 3. Part 3: n=■ (25 mg starting dose: n=■; all starting doses: n=■)
Sample size, power calculation	For Part 2, approximately 204 participants provided >90% power to detect a mean change of TSS of -10 in the placebo + SDT group versus -19.7 in the avapritinib + SDT group, assuming a SD of 20 and using a one-sided type I error rate of 0.025 with a two-sample t-test
Statistical analysis	Primary endpoint (Part 2): ANCOVA for mean change in ISM-SAF TSS from baseline to week 24, controlling for randomisation stratification factors (serum tryptase <20 versus ≥20 ng/mL and baseline ISM severity [moderate versus severe]). One-sided p-value <0.025 defined statistical significance. Key secondary endpoints (Part 2): Tested hierarchically using a gatekeeping procedure to control family-wise Type I error at 0.025. The Cochran-Mantel-Haenszel test was used for binary endpoints, controlling for the same stratification factors. Descriptive statistics: Mean, SD, median, minimum, and maximum for continuous variables; frequencies and percentages for categorical variables.
Efficacy analysis	Subgroup analyses: Included analyses by baseline tryptase level (<20 versus ≥20 ng/mL), baseline TSS severity (moderate versus severe), age, sex, and geographic region. Sensitivity analyses: PP analysis and alternative approaches to missing data handling to assess robustness of primary findings. OLE: Part 3 baseline definitions varied by patient treatment history: for participants who received avapritinib in Parts 1 or 2, baseline was the time of avapritinib initiation; for participants who received placebo in Parts 1 or 2, baseline was defined as the start of Part 3. For dose escalation analysis, baseline was defined as the last value prior to dose escalation to 50 mg.
Data management, patient withdrawals	Participants could withdraw from the study at any time. Participants who discontinued treatment were encouraged to complete all remaining scheduled visits. For participants who discontinued treatment or withdrew from the study, all available data up to the point of discontinuation were included in analyses. Missing data approach: If a patient was missing >7 days of scores in the 14 days before baseline or week 24, the respective score was considered missing. Participants with high-dose steroid use within 7 days before week 24 or >14 consecutive days at any point from baseline to week 24 were excluded from the primary efficacy analysis. No imputation was performed for the primary analysis; sensitivity analyses used various approaches to assess the impact of missing data.
Source: Adapted from Table 12, CS¹ ANCOVA = analysis of covariance; BM = bone marrow; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; MC = mast cells; OLE = open-label extension; PP = per-protocol; QD =	

Trial number (acronym)	NCT03731260 (PIONEER)
once daily; SAF = Symptom Assessment Form; SD = standard deviation; SDT = symptom-directed therapy; TSS = total symptom score; VAF = variant allele frequency	

The participant flow throughout the entirety of the PIONEER trial is detailed below.

Figure 3.3: CONSORT diagram of PIONEER clinical study participants



Source: Adapted from Figure 2, CS Appendices¹⁰

AE = adverse event; CONSORT = CONSolidated Standards of Reporting Trials; CS = company submission; DCO = data cut-off

3.2.4 Baseline characteristics of PIONEER trial

The baseline characteristics reported for Part 2 of PIONEER are shown below.

Table 3.5 Key baseline characteristics in PIONEER Part 2

Parameter	Avapritinib 25 mg (N=141)	Placebo (N=71)
Demographics		
Female, n (%)	100 (70.9)	54 (76.1)
Age, years, mean (SD)	48.7 (11.70)	52.2 (12.52)
Age < 65 years, n (%)	132 (93.6)	60 (84.5)
White, n (%)	109 (77.3)	61 (85.9)
Not Hispanic or Latino, n (%)	99 (70.2)	58 (81.7)
Weight, kg, mean (SD)	81.12 (17.92)	82.19 (17.80)
BMI, kg/m ² , mean (SD)	28.31 (5.4)	29.46 (5.28)
Disease characteristics		
Mean (SD) ISM-SAF TSS	50.17 (19.15)	52.43 (19.82)
ISM-SAF TSS ≥42 (severe), n (%)	87 (61.7)	45 (63.4)
Median (min, max) serum tryptase, ng/mL	38.40 (3.6, 256.0)	43.70 (5.7, 501.6)
Median (min, max) <i>KIT</i> D816V MAF	0.39 (0.00, 41.29)	0.26 (0.00, 36.74)
Median (Min, Max) BM MCs, %	7.00 (1.0, 50.0)	7.00 (1.0, 70.0)

Parameter	Avapritinib 25 mg (N=141)	Placebo (N=71)
Median (min, max) mast cells in skin (lesional), count/mm ²	459.0 (89, 2870)	617.5 (83, 2609)
Most common medical history, n (%)		
Gastrointestinal disorders	114 (80.9)	55 (77.5)
Musculoskeletal and connective tissue disorders	112 (79.4)	58 (81.7)
Skin and subcutaneous tissue disorders	110 (78.0)	52 (73.2)
Source: Table 10, CS BM = bone marrow; BMI = body mass index; CS = company submission; ISM = indolent systemic mastocytosis; MAF = mutant allele fraction; Max = maximum; MCs = mast cells; Min = minimum; SAF = Symptom Assessment Form; SD = standard deviation; TSS = total symptom score		

EAG comment: The groups in Part 2 of PIONEER seem to be well balanced. However, there is a question of generalisability, and so the EAG requested the data for Europe and the UK separately, which the company provided in response to the clarification letter (see Table 3.6).⁵ This showed that UK patients seemed to have more severe disease with a higher ECOG PS, serum tryptase and greater number of mast cells. The only one of these characteristics to be examined in a subgroup analysis, baseline serum tryptase, showed a larger point estimate in the treatment effect with higher levels, although based on a very small sample size for serum tryptase <20 ng/mL. (see Section 3.2.8). Also, the company clinical experts did state that PIONEER was generalisable to UK clinical practice, and one explicitly mentioned “tryptase”.⁶

Table 3.6 Demographic and baseline characteristics of PIONEER participants in Europe and the UK

Characteristic	Europe overall (N=■)	United Kingdom (N=■)
Mean age (years)	■	■
Age group <65 years	■	■
Sex (female)	■	■
Race (white)	■	■
Mean BMI (kg/m ²)	■	■
ECOG PS 0	■	■
ECOG PS 1	■	■
ECOG PS 2	■	■
Median serum tryptase (ng/mL)	■	■
Tryptase 20 ng/mL	■	■
Mean BM mast cells (%)	■	■
Mean <i>KIT D816V</i> MAF (digital PCR)	■	■
History of anaphylaxis	■	■
Prior cytoreductive therapy	■	■
Prior TKI therapy	■	■
Source: Tables 2 and 3, clarification response ⁵ BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; PCR = polymerase chain reaction; PS = Performance Status; TKI = tyrosine kinase inhibitor; UK = United Kingdom		

The EAG also requested a comparison of SDT use between PIONEER and UK clinical practice, which the company provided with the latter being based on their clinical expert opinion.⁵ This is shown in Table 3.7, into which have been placed the EAG clinical expert responses. As can be seen there are discrepancies between PIONEER and the clinical experts, which could have some effect on the treatment effect of avapritinib when added to SDT, which implies that the generalisability of PIONEER is identified as a Key Issue. Note that there is further discussion of the basket of SDT in the cost effectiveness (CE) Section below.

Table 3.7: Symptom-directed treatment basket

Comparator	% of patients in avapritinib + SDT arm (PIONEER) ^{4, 28}	% of patients in placebo + SDT arm (PIONEER) ^{4, 28}	% of patients in SDT (UK clinical practice)	Justification	EAG clinical expert (SM)	EAG clinical expert (SW) – SDT + avapritinib	EAG clinical expert (SW) – SDT only
H1-blockers (average)	████	████	████ usage on H1-blockers, includes desloratadine, fexofenadine, cetirizine and loratadine (see Table 55 in the CS).	Validated by three UK clinical experts. ⁵ One clinical expert from secondary engagement also proposed that 90% usage of H1-blockers is, on average.	100%	90%	90-95%
H2-blocker (cimetidine)	████	████	████ usage on H2-blockers, commonly used famotidine, cimetidine, and nizatidine. According to the follow-up clinical expert engagement, ranitidine was previously very commonly used but the discovery of NDMA in some formulations led to most patients discontinuing it around 2020.	Ranitidine was included in the PIONEER but excluded from the analysis due to safety concerns. ^{23, 40} The proportion of H2-blocker usage was validated by three UK clinical experts. ⁵ One clinical expert from secondary engagement proposed that 80-90% usage of H2-blockers. Ranitidine is discontinued in the UK, and its market authorisation was suspended by the MHRA and EMA due to it associated safety risk. ^{40, 41}	70%	50-60%	50-60%
PPI (omeprazole)	████	████	████	Validated by three UK clinical experts. ⁵ One clinical expert from secondary engagement	50%	10%	20%

Comparator	% of patients in avapritinib + SDT arm (PIONEER) ^{4, 28}	% of patients in placebo + SDT arm (PIONEER) ^{4, 28}	% of patients in SDT (UK clinical practice)	Justification	EAG clinical expert (SM)	EAG clinical expert (SW) – SDT + avapritinib	EAG clinical expert (SW) – SDT only
				proposed that 30-40% usage of PPI.			
Leukotriene inhibitor (montelukast)	████	████	████	Validated by three UK clinical experts. ⁵ One clinical expert proposed that possibly around █████ usage of montelukast, and from secondary engagement proposed less than 20% usage.	50%	10-40%	10-40%
Corticosteroid (prednisolone)	████	████	████	Agreed and validated by three UK clinical experts. ⁵	10%	0% („short term use“)	0% („short term use“)
Cromolyn sodium (nalcrom)	████	████	████	Validated by three UK clinical experts. ⁵ One clinical expert thought that Nalcrom possibly have a usage of around █████ and from secondary engagement, the clinical expert proposed █████ usage.	30%	5-10%	5-10%
Monoclonal antibody (omalizumab)	████	████	██	One clinical expert thought █████ usage is sound, one clinical expert was not sure, and another one thought █████ usage seems too high, but did not provide a validated value. ⁵	<5%	0%	5%

Comparator	% of patients in avapritinib + SDT arm (PIONEER) ^{4, 28}	% of patients in placebo + SDT arm (PIONEER) ^{4, 28}	% of patients in SDT (UK clinical practice)	Justification	EAG clinical expert (SM)	EAG clinical expert (SW) – SDT + avapritinib	EAG clinical expert (SW) – SDT only
Loperamide	Not used in the PIONEER trial	Not used in the PIONEER trial	██████	Not included in the analysis, as loperamide was not included in the PIONEER.	N/A	N/A	N/A

Source: Table 4, clarification letter response⁵

CS = company submission; EAG = External Assessment Group; EMA = European Medicines Agency; MHRA = Medicines and Healthcare Products Regulatory Agency; N/A = not applicable; PPI = proton-pump inhibitor; SDT = symptom-directed therapy; SM = systemic mastocytosis; UK = United Kingdom

3.2.5 Efficacy results of PIONEER trial – Part 1: Dose escalation trial

In Section 2.7.1 of the CS, Part 1 of the PIONEER study was described as a dose finding component that evaluated three dose levels of avapritinib (25 mg, 50 mg, and 100 mg QD) compared with placebo in participants with ISM. [REDACTED] participants were enrolled in each avapritinib dose group, and [REDACTED] participants received placebo.¹ The primary objective of this study part was to inform selection of the RP2D.

The company reported that greater symptom reduction in ISM-SAF TSS was observed at week 12 in the 100 mg group; however, treatment effects appeared to plateau thereafter. By week 24, reductions in symptom burden were reported to be broadly similar between the 25 mg and 50 mg dose groups. Based on these findings, the company selected avapritinib 25 mg QD as the RP2D for subsequent parts of the PIONEER study.¹ Further details can be found in Tables 3.8 and 3.9 below.

Table 3.8: Mean change in ISM-SAF TSS from baseline to week 24 (PIONEER Part 1 ITT Population)

Parameter, mean (SD)	Placebo N=[REDACTED]	25 mg QD N=[REDACTED]	50 mg QD N=[REDACTED]	100 mg QD N=[REDACTED]
Baseline	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Week 12 change	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Week 24 change	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 13 of the CS ¹ CS = company submission; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; ITT = intention-to-treat; QD = once daily; SD = standard deviation; TSS = total symptom score				

Table 3.9: Percentage change in mast cell burden measures at week 12 (PIONEER Part 1 ITT Population)

Measure	Placebo N=[REDACTED]	25 mg QD N=[REDACTED]	50 mg QD N=[REDACTED]	100 mg QD N=[REDACTED]
Serum tryptase (%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BM MCs (%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<i>KIT</i> D816V allele fraction (%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 14 of the CS ¹ BM = bone marrow; CS = company submission; ITT = intention-to-treat; MCs = mast cells; QD = once daily				

EAG comment: Part 1 of the PIONEER study was exploratory in nature and included a small number of participants per dose group, limiting the robustness of the findings. However, there does appear to be a lack of a clear and consistent dose-response relationship, particularly at later time points. This is illustrated in Table 3.8, particularly at week 24, which shows similar reductions in ISM-SAF TSS. Table 3.9 also shows reductions from baseline in serum tryptase levels, BM MC burden, and *KIT* D816V allele fraction across all avapritinib dose groups, with no consistent dose-response relationship observed at week 12.

The EAG requested that the company provide further justification for selecting the 25 mg avapritinib dose, rather than the 50 mg dose, for comparison with placebo in Part 2. To support the assessment of dose selection, the EAG requested:

- a) any quantitative comparisons of efficacy outcomes between the 25 mg and 50 mg dose groups in Part 1; and
- b) the rationale for deprioritising the 50 mg dose, particularly if it demonstrated comparable or greater early symptom reduction.

The company responded to point (a) that⁵ “Patients who received avapritinib 25 mg and 50 mg demonstrated that while higher doses showed slightly greater reductions in some objective biomarkers compared to placebo, TSS reduction was comparable by the 24 week analysis”. Further details of week 24 results can be found in Table 3.10.

Table 3.10: Quantitative comparison of efficacy outcomes in PIONEER Part 1

Efficacy parameter	Avapritinib 25 mg (N=)	Avapritinib 50 mg (N=)
50% reduction in serum tryptase (week 24)		
50% reduction in <i>KIT</i> D816V MAF (week 24)		
50% reduction in BM MCs (week 24)		
Based on Table 7 of the clarification letter ⁵ BM = bone marrow; KIT = KIT proto-oncogene receptor tyrosine kinase; MAF = mutant allele fraction; MCs = mast cells; mg = milligram; N = number of individuals in the analysis		

In response to point (b), the company stated that⁵ “The decision to select 25 mg once daily as the RP2D rather than 50 mg once daily was based on an integrated assessment of benefit-risk, safety and the chronic nature of ISM.

The 25 mg cohort demonstrated exceptional safety that was similar to placebo. During Part 1, the 25 mg group experienced no Grade 3 or greater AEs, no dose modifications and no early discontinuations due to AEs. In contrast, one patient in the 50 mg group discontinued treatment due to an AE.

Further, unlike AdvSM, which is malignant and fatal, ISM is a non-malignant condition where people with the disease typically have a preserved life expectancy but suffer from lifelong, debilitating symptoms. Consequently, the benefit-risk assessment favoured the most well-tolerated, lowest effective dose to ensure patients could remain on therapy long-term.

Although the 100 mg dose demonstrated the fastest initial symptom reduction, it plateaued after Week 12. By Week 24, the 25 mg and 50 mg doses achieved comparable reductions in TSS, suggesting that the lower dose was sufficient to achieve substantial clinical benefit without the potential for dose-related toxicities.

The primary treatment goal in ISM is the reduction of symptom burden and improvement in QoL. Since 25 mg once daily effectively reduced both symptoms and all objective measures of mast cell burden while maintaining a superior safety profile, it was considered the most appropriate dose for comparison with placebo in the pivotal Part 2 of the study.”.

In conclusion, the EAG considers that the reductions in symptom and mast cell burden were broadly similar between the 25 mg and 50 mg dose groups. In the absence of a clear dose-response relationship, the choice of the lower dose reflects considerations around long-term treatment and safety.

3.2.6 Efficacy results of PIONEER trial – Part 2: Double-blind, placebo-controlled RCT

3.2.6.1 Symptom burden assessed using the ISM-SAF

3.2.6.1.1 Change in overall symptom score (ISM-SAF TSS) from baseline to Week 24: Avapritinib vs placebo

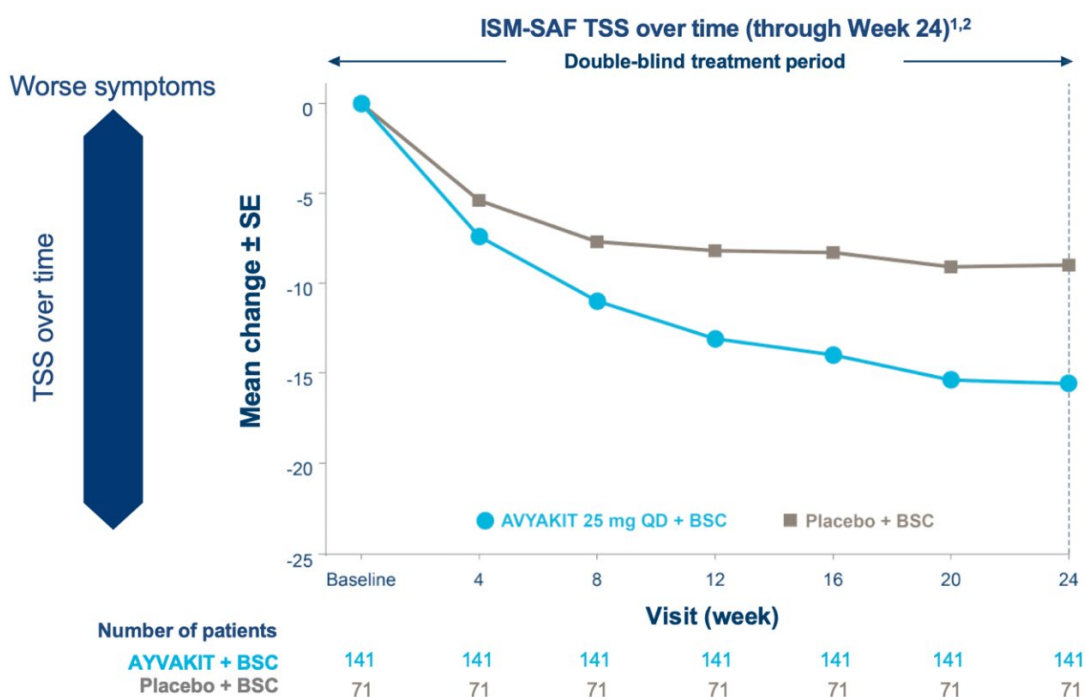
The company reported that the LS mean (standard error [SE]) change from baseline at week 24 in ISM-SAF TSS was - [REDACTED] with avapritinib 25 mg compared with [REDACTED] with placebo, resulting in a statistically significant between-group difference of [REDACTED]. Over time, ISM-SAF TSS initially decreased in both groups, plateaued in the placebo group, and continued to improve in the avapritinib group. Further details are presented in Table 3.11 and Figure 3.4. Sensitivity analyses for missing data were consistent with the primary analysis, and analyses in the PP population showed similar between-group differences.^{1, 11, 12}

Table 3.11: Mean change in TSS of ISM-SAF from baseline to week 24 (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg (N=141)	Placebo (N=71)
Baseline, Mean (SD)	50.17 (19.15)	52.43 (19.82)
Week 24, Mean (SD)	33.48 (20.06)	42.32 (21.03)
CFB, LS Mean (SE)	-15.58 (1.54)	-9.15 (2.01)

Based on Table 15 of the CS¹
 CFB = change from baseline; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; LS = least squares; SAF = Symptom Assessment Form; SD = standard deviation; SE = standard error; TSS = total symptom score

Figure 3.4: Change from baseline of ISM-SAF TSS at week 24 (PIONEER Part 2 ITT population)



Based on Figure 13 of the CS¹

Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

BSC = best supportive care; CS = company submission; ISM = indolent systemic mastocytosis; SAF = Symptom Assessment Form; ITT = intention-to treat; LS Mean = least squares mean; SDT = symptom-directed therapy; TSS = total symptom score

3.2.6.1.2 Patients with ISM achieving 30% and 50% reductions in TSS at Week 24: Avapritinib vs placebo

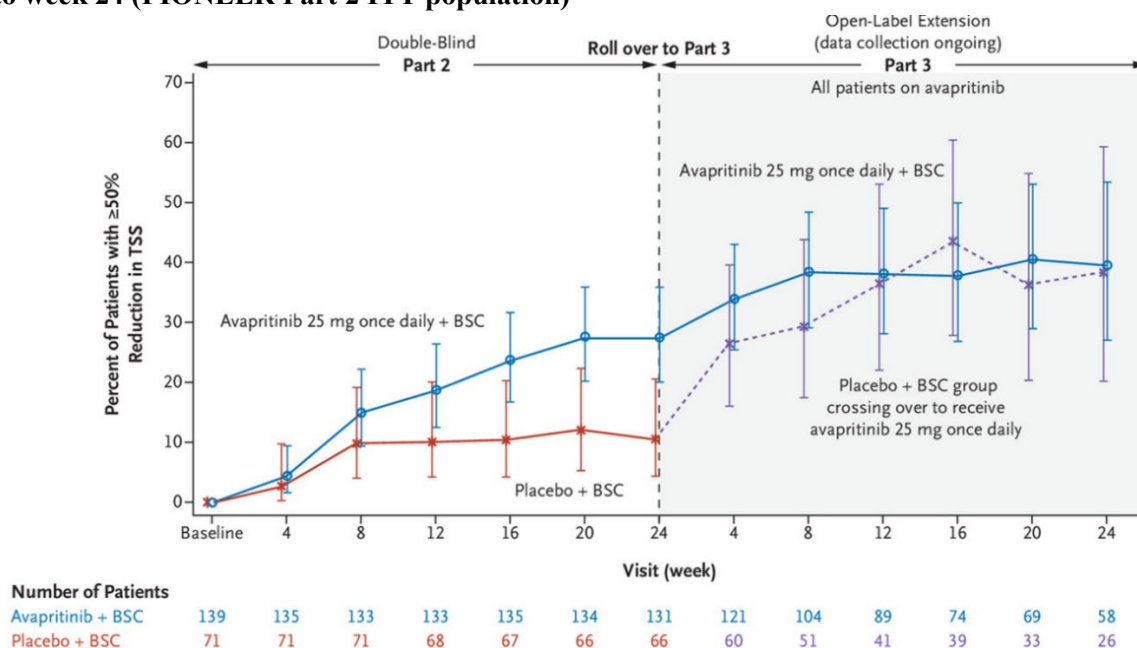
The company reported that a greater proportion of participants in the avapritinib group achieved clinically meaningful reductions in TSS ($\geq 30\%$ and $\geq 50\%$) at week 24 compared with placebo. For the $\geq 50\%$ reduction threshold, 24.8% of participants receiving avapritinib achieved this level of improvement compared with 9.9% in the placebo group (odds ratio [OR]: 3.10; 95% confidence interval [CI]: 1.24, 8.64; $p=0.005$). For the $\geq 30\%$ threshold, the corresponding proportions were 45.4% and 29.6%, respectively (OR: 2.07; 95% CI: 1.08, 3.99; $p=0.009$). Further details can be found in Table 3.12. Increases over time in the proportions of participants achieving $\geq 50\%$ and $\geq 30\%$ reductions in TSS are illustrated in Figures 3.5 and 3.6, respectively. Sensitivity analyses excluding participants with missing baseline or week 24 TSS values, those who used high-dose steroids, and analyses conducted in the per-protocol (PP) population were consistent with the primary results.¹

Table 3.12: Proportion of participants with $\geq 50\%$ and $\geq 30\%$ reduction in ISM-SAF TSS at week 24 (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg N=141 n/N (%) (95% CIs)	Placebo N=71 n/N (%) (95% CI)	OR (95% CI)	P-Value
$\geq 50\%$ reduction in TSS	35/141 (24.8) (17.9, 32.8)	7/71 (9.9) (4.1, 19.3)	3.10 (1.24, 8.64)	0.005
$\geq 30\%$ reduction in TSS	64/141 (45.4) (37.0, 54.0)	21/71 (29.6) (19.3, 41.6)	2.07 (1.08, 3.99)	0.009

Based on Table 16 of the CS¹
 CI = confidence interval; CS = company submission; ISM = indolent systemic mastocytosis; OR = odds ratio; SAF = Symptom Assessment Form; ITT = intention-to-treat; TSS = total symptom score

Figure 3.5: Percentage of participants with $\geq 50\%$ reduction in the ISM-SAF TSS from baseline to week 24 (PIONEER Part 2 ITT population)

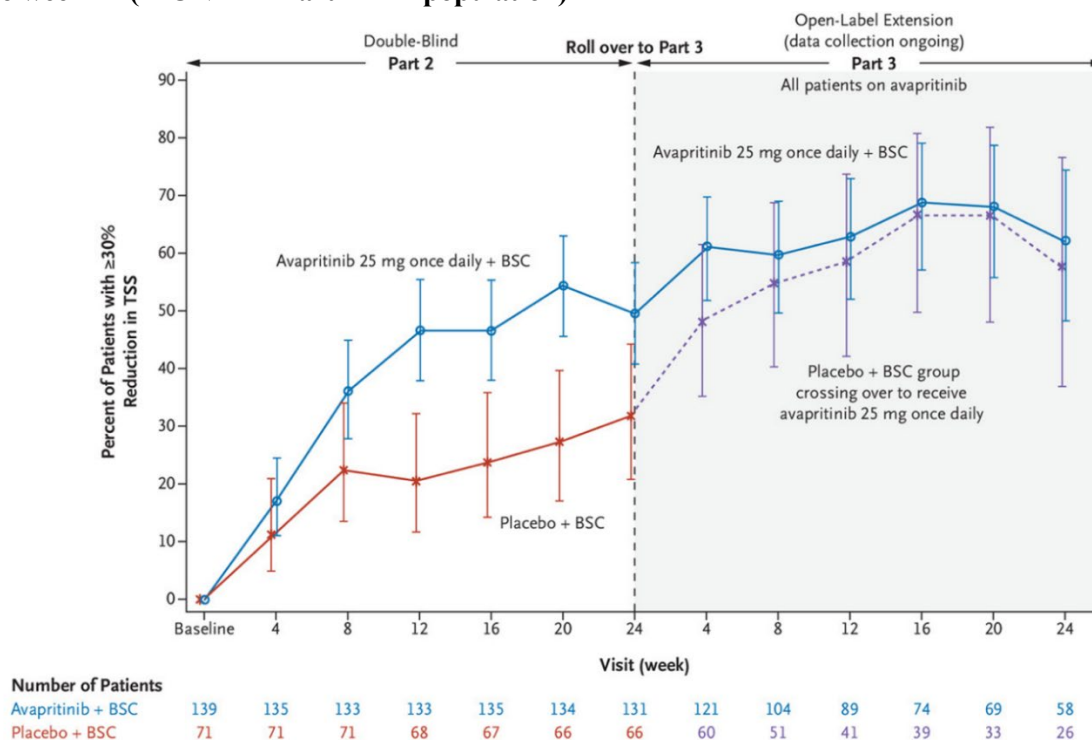


Based on Figure 14 of the CS.¹

Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

BSC = best supportive care; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; SAF = Symptom Assessment Form; SDT = symptom-directed therapy; TSS = total symptom score

Figure 3.6: Percentage of participants with $\geq 30\%$ reduction in the ISM-SAF TSS from baseline to week 24 (PIONEER Part 2 ITT population)



Based on Figure 15 of the CS¹

BSC = best supportive care; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; SAF = Symptom Assessment Form; SDT = symptom-directed therapy; TSS = total symptom score

Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

3.2.6.1.3 Changes in ISM-SAF domain scores from baseline to Week 24: Avapritinib vs placebo

The company reported changes in key ISM-SAF domains at week 24, including gastrointestinal, skin, and neurocognitive symptoms. Further details are presented in Table 3.13. The skin domain showed the largest difference between treatment groups, with a mean (standard deviation [SD]) change from baseline of -5.87 (6.49) for avapritinib compared with -2.64 (4.11) for placebo (difference: -3.23; 95% CI: -4.73, -1.73; $p < 0.0001$). The company also reported¹ “Among individual symptoms, statistically significant differences favouring avapritinib were observed for spots severity ($p < 0.0001$), itching severity ($p < 0.0001$), and flushing severity ($p = 0.009$) at week 24”.

Table 3.13: Changes in key domains of ISM-SAF at week 24 (PIONEER Part 2 ITT population)

Domain/cluster	Avapritinib 25 mg N=131 Mean (SD) change	Placebo N=66 Mean (SD) change	Difference (95% CI)	p-value
GI domain	-3.74 (4.87)	-3.14 (4.67)	-0.60 (-2.03, 0.83)	0.410
Skin domain	-5.87 (6.49)	-2.64 (4.11)	-3.23 (-4.73, -1.73)	< 0.0001
Neurocognitive symptom cluster	-4.03 (5.22)	-2.81 (4.29)	-1.22 (-2.69, 0.25)	0.102

Based on Table 17 of the CS¹

Domain/cluster	Avapritinib 25 mg N=131 Mean (SD) change	Placebo N=66 Mean (SD) change	Difference (95% CI)	p-value
CI = confidence interval; CS = company submission; GI = gastrointestinal; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; SAF = Symptom Assessment Form; SD = standard deviation				

3.2.6.2 Objective measures of mast cell burden at week 24: Avapritinib versus placebo

The company reported objective measures of mast cell burden from baseline to week 24, focusing on the proportion of participants achieving a $\geq 50\%$ reduction. Mean changes showed significantly greater reductions with avapritinib than with placebo in serum tryptase, *KIT D816V* MAF, and BM MC burden. The proportion of participants achieving a $\geq 50\%$ reduction was significantly higher with avapritinib across all measures ($p < 0.0001$ for all comparisons).¹ Further details are provided in Table 3.14.

According to the company, post hoc analyses indicated that among participants with baseline serum tryptase ≥ 20 ng/mL, more than half of those treated with avapritinib achieved normalisation, with approximately half reaching levels below the limit of detection. Similarly, [REDACTED] of avapritinib-treated participants with BM aggregates at baseline had no aggregates at week 24. For *KIT D816V*, [REDACTED] of participants with baseline mutant allele fraction (MAF) $\geq 1\%$ achieved a reduction to $< 1\%$ with avapritinib, whereas no participants in the placebo group reached this threshold. These findings were consistent across sensitivity analyses in the PP population.¹

Table 3.14: Objective measures of mast cell burden at week 24 (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg N=141	Placebo N=71	Difference/OR (95% CI)	P-Value
Mean (SD) change from baseline				
Serum tryptase (ng/mL)	[REDACTED]	[REDACTED]	-	-
<i>KIT D816V</i> MAF (%)	[REDACTED]	[REDACTED]	-	-
BM MCs (%)	[REDACTED]	[REDACTED]	-	-
Response rates: n/N (%) (95% CI)				
$\geq 50\%$ reduction in serum tryptase	76/141 (53.9) (45.3, 62.3)	0/71 (0.0) (0.0, 5.1)	OR: NE (30.59, NE)	< 0.0001
$\geq 50\%$ reduction in <i>KIT D816V</i> MAF or undetectable	80/118 (67.8) (58.6, 76.1)	4/63 (6.3) (1.8, 15.5)	OR: 39.34 (10.93, 140.56)	< 0.0001
$\geq 50\%$ reduction in BM MCs or no aggregates	56/106 (52.8) (42.9, 62.6)	13/57 (22.8) (12.7, 35.8)	OR: 4.74 (2.06, 11.45)	< 0.0001
Post-hoc analyses: n/N (%)				
Normalisation of tryptase (< 20 ng/mL)	58/107 (54.0)	1/50 (2.0)	-	-
Tryptase below LLD (< 11.4 ng/mL)	29/107 (27.1)	0/50 (0.0)	-	-
Undetectable <i>KIT D816V</i> MAF ($< 0.02\%$)	12/109 (11.0)	3/54 (6.0)	-	-
Reduction to <i>KIT D816V</i> MAF $< 1\%$	14/40 (35.0)	0/22 (0.0)	-	-
No BM MC aggregates	33/91 (36.0)	6/50 (12.0)	-	-

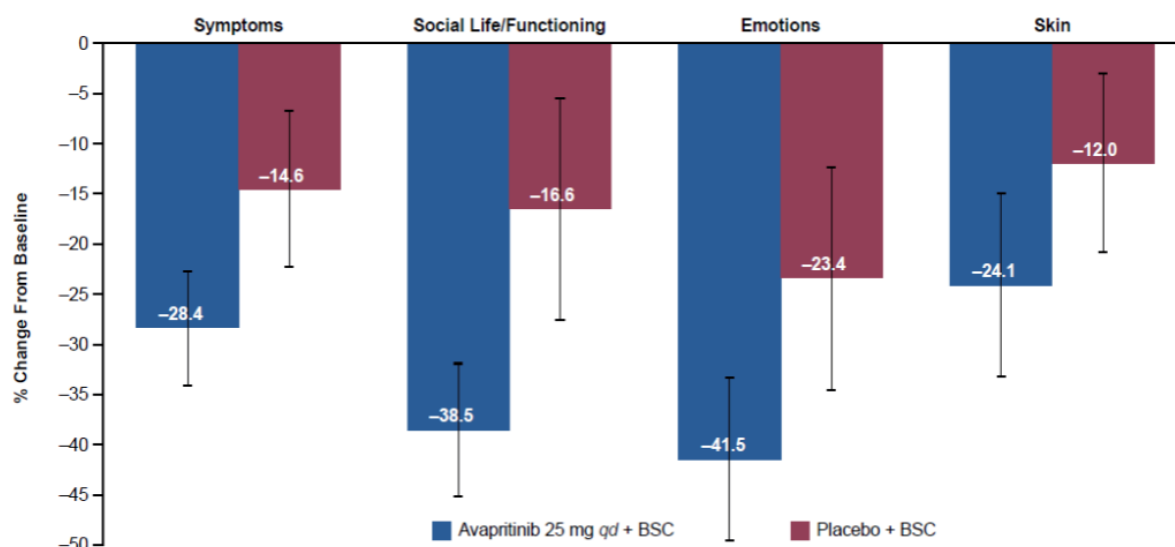
Parameter	Avapritinib 25 mg N=141	Placebo N=71	Difference/OR (95% CI)	P-Value
Based on Table 18 of the CS ¹ BM = bone marrow; CI = confidence interval; CS = company submission; ITT = intention-to-treat; LLD = lower limit of detection; MAF = mutant allele fraction; MCs = mast cells; NE = not evaluable; OR = odds ratio; SD = standard deviation				

3.2.6.3 Health-related quality of life (HRQoL) in PIONEER randomised phase

3.2.6.3.1 MC-QoL at 24 weeks: avapritinib vs placebo

The company reported that mean total MC-QoL scores were similar between treatment groups at baseline: 57.50 (16.02) for avapritinib and 57.47 (17.20) for placebo. The MC-QoL is a 27-item mastocytosis-specific instrument, with higher scores indicating greater impairment (range 0–100). By week 24, participants treated with avapritinib showed greater improvements across all domains compared with placebo. The largest mean percentage reductions with avapritinib were observed in the emotions domain (-41.47%) and social life/functioning domain (-38.52%). Further details are presented in Figure 3.7. A post-hoc sensitivity analysis excluding French translations (due to mistranslation issues) produced results consistent with the primary analysis.¹

Figure 3.7: Change in MC-QoL from baseline at week 24 (PIONEER Part 2 ITT population)



Based on Figure 16 of the CS¹

BSC = best supportive care; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; MC-QoL = Mastocytosis Quality of Life Questionnaire; SD = standard deviation; SDT = symptom-directed therapy

Note: BSC refers to SDT and includes symptom-directed therapies used for ISM.

3.2.6.3.2 PGIS and PGIC at 24 weeks: Avapritinib vs placebo

The company stated that the PGIS measures disease severity on a 0-4 scale, with lower scores indicating improvement, while the PGIC measures overall improvement on a 1-7 scale, with higher scores indicating greater improvement.¹ According to the company, mean (SD) PGIS scores were identical at baseline in both groups (██████ for avapritinib and ██████ for placebo). By week 24, participants treated with avapritinib showed a greater reduction in PGIS than those receiving placebo

(mean change: [REDACTED]). PGIC was assessed post-baseline only, with avapritinib-treated participants reporting greater improvement than placebo at all time points. At week 24, the mean (SD) PGIC score was [REDACTED] with avapritinib and [REDACTED] with placebo, corresponding to moderate and minimal improvement, respectively.¹ Further details can be found in Table 3.15.

Table 3.15: Change in PGIS and PGIC from baseline at week 24 (PIONEER Part 2 ITT population)

Measure	Avapritinib 25 mg	Placebo
PGIS		
N	[REDACTED]	[REDACTED]
Baseline mean (SD)	[REDACTED]	[REDACTED]
Change from baseline mean (SD)	[REDACTED]	[REDACTED]
PGIC		
N	[REDACTED]	[REDACTED]
Score at week 24 (SD)	[REDACTED]	[REDACTED]
Based on Table 19 of the CS ¹ CS = company submission; ITT = intention-to-treat; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SD = standard deviation		

3.2.6.3.3 SF-12 at 24 weeks: Avapritinib vs placebo

The company stated that the SF-12 measures HRQoL, generating Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, with higher scores indicating improvement.¹ Mean PCS and MCS scores were comparable between groups at baseline. By week 24, participants treated with avapritinib showed greater improvements in both components than those receiving placebo. The mean percentage increase in PCS was 19.95% with avapritinib versus 12.14% with placebo, while the MCS increased by 12.34% versus 6.28%, respectively.¹ Further details are provided in Table 3.16.

Table 3.16: Change in SF-12 from baseline at week 24 (PIONEER Part 2 ITT population)

SF-12 component	Avapritinib 25 mg N=120	Placebo N=59
Physical component summary		
Baseline: mean (SD)	33.83 (10.79)	34.07 (10.70)
Mean (SD) change	5.60 (8.43)	3.08 (7.01)
Mean (SD) percent change	19.95 (30.90)	12.14 (26.59)
Mental component summary		
Baseline: Mean (SD)	40.60 (10.51)	40.99 (10.67)
Mean (SD) change	3.92 (9.27)	1.62 (9.03)
Mean (SD) percent change	12.34 (26.57)	6.28 (26.93)
Based on Table 20 of the CS ¹ CS = company submission; ITT = intention-to-treat; SD = standard deviation; SF-12 = 12-item Short Form Health Survey		

3.2.6.3.4 EQ-5D-5L (VAS) at 24 weeks: Avapritinib vs placebo

The company stated that the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L) (visual analogue scale [VAS]) measures self-rated health on a 0–100 scale, with higher scores indicating improvement. Mean (SD) VAS scores were similar between groups at baseline. By week 24,

participants treated with avapritinib showed greater improvement than those receiving placebo, with a mean increase of 6.6 points (18.5% improvement) versus 0.1 points (4.5% improvement), respectively.¹ Further details are provided in Table 3.17.

Table 3.17: Change in EQ-5D-5L (VAS) from baseline at week 24 (PIONEER Part 2 ITT population)

Measure	Avapritinib 25 mg	Placebo
EQ-5D-5L (VAS)		
N	121	59
Baseline mean (SD)	57.2 (17.61)	55.9 (17.85)
Change from baseline mean (SD)	6.6 (18.84)	0.1 (13.58)
Percent change from baseline mean (SD)	18.5% (48.83%)	4.5% (32.29%)
Based on Table 21 of the CS ¹ CS = company submission; EQ-5D-5L = EuroQoL 5-Dimension 5-Level questionnaire; ITT = intention-to-treat; SD = standard deviation; VAS = visual analogue scale		

3.2.6.4 Anaphylaxis frequency at week 24: Avapritinib vs placebo

The company reported exploratory analyses of anaphylaxis episodes in a subset of 13 PIONEER participants who required epinephrine (10 avapritinib; 3 placebo). Among avapritinib-treated patients, 8 of 10 who experienced anaphylaxis during the 12-week screening period had no events during the 24-week treatment period. In contrast, all three placebo patients experienced anaphylaxis only during treatment, with no events during screening. During Part 2, event rates ranged from 0.00 to 0.67 events per month in the avapritinib group and from 0.17 to 0.67 events per month in the placebo group¹.

3.2.6.5 Symptom-directed therapy medication usage at 24 weeks: Avapritinib vs placebo

According to the company, avapritinib reduced SDT medication use compared with placebo at week 24. Overall, 21% (30/141) of patients receiving avapritinib decreased SDT use versus 13% (9/71) receiving placebo. In addition, 3% (4/141) of patients in the avapritinib group completely discontinued SDT (including one patient receiving five SDTs at baseline), compared with none in the placebo group.

EAG comment: Overall, there were better outcomes with avapritinib 25 mg than placebo, including statistically significant differences in change in overall symptom score (ISM-SAF TSS), and proportion achieving both $\geq 30\%$ and $\geq 50\%$ reduction in TSS. The sensitivity and exploratory analyses presented by the company were broadly consistent with the primary efficacy findings from Part 2, with improvements favouring avapritinib 25 mg over placebo. However, treatment effects were not observed consistently across all ISM-SAF symptom domains, with improvements primarily driven by the skin domain, suggesting potential heterogeneity of effect across symptoms. This might be a concern if patients become eligible for avapritinib because their symptoms are predominantly not skin-related or those of the skin not the most severe. Indeed, the baseline characteristics of Part 2 of PIONEER show that a high percentage of patients (about 80%) have symptoms that are not skin-related (see Section 3.2.4), although it is unclear as to the degree of overlap between the various domains. This is therefore regarded as a Key Issue by the EAG.

Although reductions in mast cell burden and improvements in HRQoL were reported with avapritinib, between-group comparative effect estimates were not consistently reported, which could limit inference. However, the magnitude of difference in point estimates was generally quite large. The sensitivity analysis excluding French translations of the MC-QoL questionnaire was reported to be

consistent with the main analysis, although limited detail was provided. Exploratory analyses of anaphylaxis were based on very small numbers and should therefore be interpreted with caution.

The EAG requested that the company provide further information on the MC-QoL data, specifically regarding the statement that “a post-hoc sensitivity analysis excluding French translations (due to mistranslation issues) was consistent with the overall analysis”. To confirm this consistency, the EAG requested additional details on the nature and extent of the mistranslation issues, as well as the full results of the analysis both including and excluding the French translations. The company responded that:⁵ “Overall, a greater reduction in MC-QoL percentage change from baseline was observed in the full ITT population for avapritinib [REDACTED] vs placebo group [REDACTED]. Following the post-hoc sensitivity analysis (exclusion of French mistranslations), MC-QoL was similarly affected by avapritinib treatment [REDACTED] compared to placebo control group [REDACTED]” Further details can be found in Table 17 of the clarification letter response, but they are not reproduced here for brevity, considering the consistency with the full ITT population results.

In response to a request by the EAG, the company provided data on SDT use in the placebo arm at 24 weeks, showing that mean SDT use remained largely unchanged from baseline (mean [REDACTED]) to week 24 (mean [REDACTED]), corresponding to a mean change from baseline of [REDACTED]. Further details can be found in Table 3.18. Overall, the results show that patients treated with avapritinib were more likely to reduce or discontinue SDT.

Table 3.18: PIONEER Part 2 change from baseline in SDT use

Parameter	Part 2 ITT population	
	Placebo (N=71)	Avapritinib 25 mg (N=141)
Baseline		
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]
C7D1	[REDACTED]	[REDACTED]
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]
C7D1 (24 weeks) change from baseline		
Mean (SD)	[REDACTED]	[REDACTED]
Median (Min, Max)	[REDACTED]	[REDACTED]
Based on Table 6 of the clarification letter ⁵ C = cycle; D = day; ITT = intention-to-treat; Max = maximum; Min = minimum; SD = standard deviation; SDT = symptom-directed therapy; SM = systemic mastocytosis Notes: Concomitant SDT medications are all medications used to manage symptoms of SM and taken at any time from first dose date of study drug to last dose date of study drug + 30 days. Baseline SDT is the number of SDT taken on C1D1. SDT at cycle 1 is number of SDT taken during C1D2 to C1D28. SDT at cycle x is number of SDT taken during cycle x, CxD1-CxD28, x=2,3, etc.		

3.2.7 Efficacy results of PIONEER trial – Part 3: Long-term open-label extension (OLE) phase

3.2.7.1 Change in overall symptom score (ISM-SAF TSS) from baseline at 1, 2 and 3 years

The company reported that, in the ITT population, avapritinib was associated with substantial and sustained reductions in ISM-related symptom severity over up to 3 years of treatment. Mean (SD) reductions from baseline in TSS were [REDACTED] points at 1 year, with sustained reductions of

points at 2 years and points at 3 years. These reductions were reported to be consistent across participants' starting doses of avapritinib. Similar results were reported for the PP population.¹ Further details are provided in Tables 3.19 and 3.20.

The company also stated that, in both the Safety and PP populations, participants who maintained a 25 mg dose at the time of data cut demonstrated comparable reductions in TSS at 1, 2, and 3 years, with similar proportions achieving clinically meaningful symptom improvements. Among participants who escalated to 50 mg, additional reductions in TSS were observed following dose escalation, with sustained improvements at 6 months and 1 year, meeting clinical criteria for dose increase.¹

Table 3.19: Change in ISM-SAF TSS from baseline up to 3 years avapritinib (PIONEER Part 3 ITT population)

Parameter	Avapritinib 25 mg starting dose (N=226)	Avapritinib all starting doses (N=)
Baseline		
N	224	
TSS, mean (SD)	48.1 (19.5)	
~ 1 year from baseline (C13 D1)		
N	195	
TSS, mean (SD)	29.6 (20.5)	
TSS change from baseline, mean (SD)	-17.7 (19.3)	
Percent TSS change from baseline, mean (SD)	-35.6 (39.0)	
~ 2 years from baseline (C25D1)		
N	165	
TSS, mean (SD)	29.6 (22.2)	
TSS change from baseline, mean (SD)	-17.5 (22.2)	
Percent TSS change from baseline, mean (SD)	-32.3 (50.1)	
~ 3 years from baseline (C40D1)		
N	129	
TSS, mean (SD)	27.9 (19.7)	
TSS change from baseline, mean (SD)	-19.4 (20.1)	
Percent TSS change from baseline, mean (SD)	-37.8 (40.1)	
Based on Table 22 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; ISM = indolent systemic mastocytosis; ITT = intention to treat; SAF = Symptom Assessment Form; SD = standard deviation; TSS = total symptom score Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3		

Table 3.20: Change in ISM-SAF TSS from baseline up to 3 years avapritinib (PIONEER Part 3 PP population)

Parameter	Avapritinib 25 mg starting dose (N=■)	Avapritinib all starting doses (N=■)
Baseline		
N	■	■
TSS, mean (SD)	■	■
~ 1 year from baseline (C13 D1)		
N	■	■
TSS, mean (SD)	■	■
TSS change from baseline, mean (SD)	■	■
Percent TSS change from baseline, mean (SD)	■	■
~ 2 years from baseline (C25D1)		
N	■	■
TSS, mean (SD)	■	■
TSS change from baseline, mean (SD)	■	■
Percent TSS change from baseline, mean (SD)	■	■
~ 3 years from baseline (C40D1)		
N	■	■
TSS, mean (SD)	■	■
TSS change from baseline, mean (SD)	■	■
Percent TSS change from baseline, mean (SD)	■	■
Based on Table 23 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; ISM = indolent systemic mastocytosis; PP = per-protocol; SAF = Symptom Assessment Form; SD = standard deviation; TSS = total symptom score Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3		

3.2.7.2 Percentage of patients with ISM achieving 30% and 50% reductions in TSS at 1, 2 and 3 years avapritinib treatment

The company reported that long-term treatment with avapritinib resulted in sustained, clinically meaningful symptom improvements, with consistent proportions of participants achieving moderate ($\geq 30\%$) and substantial ($\geq 50\%$) reductions in symptom burden at 1 year from baseline across analysis populations. In the ITT population, ■ of participants achieved a $\geq 30\%$ reduction in TSS and ■ achieved a $\geq 50\%$ reduction by 1 year. These response rates were reported to be consistent irrespective of starting dose. Comparable response rates were observed in the PP population.¹ Further details can be found in Table 3.21.

The company further stated that, among participants in the ITT and PP populations who remained on a 25 mg dose, similar proportions achieved $\geq 30\%$ and $\geq 50\%$ reductions in TSS at 1 year compared with the overall populations. Participants who escalated to 50 mg also demonstrated symptom responses from the time of dose escalation, suggesting additional benefit for those meeting clinical criteria for dose increase.¹

Table 3.21: Proportion of participants with $\geq 50\%$ and $\geq 30\%$ reduction in ISM-SAF TSS up to 3 years avapritinib (PIONEER Part 3)

Population	Avapritinib 25 mg starting dose	Avapritinib all starting doses
ITT population		
Total N	████	████
Proportion with $\geq 30\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	████████████████	████████████████
Proportion with $\geq 50\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	████████████████	████████████████
PP Population		
Total N	████	████
Proportion with $\geq 30\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	████████████████	████████████████
Proportion with $\geq 50\%$ reduction in TSS by 1 year from baseline, n (%) [95% CI]	████████████████	████████████████
Based on Table 24 of the CS ¹ CI = confidence interval; CS = company submission; ISM = indolent systemic mastocytosis; ITT = intention-to-treat; SAF = Symptom Assessment Form; TSS = total symptom score; PP = per-protocol Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The reported patient numbers were used in the calculation of mean TSS score.		

3.2.7.3 Objective measures of mast cell burden at 1, 2 and 3 years avapritinib treatment

The company reported that long-term avapritinib treatment was associated with sustained reductions in serum tryptase levels. In the ITT population, median percent reductions from baseline were █████ at 1 year and were maintained at 2 years (████) and 3 years (████), irrespective of starting dose. Although median baseline serum tryptase concentrations exceeded 20 ng/mL, meeting one of the minor diagnostic criteria for SM, median concentrations at 1, 2, and 3 years were below this threshold across all starting doses. In the PP population, median percent reductions from baseline were █████ at 1 year, maintained at 2 years (████) and 3 years (████), again irrespective of starting dose.¹ Further details can be found in Table 3.22.

The company further stated that, comparable reductions in serum tryptase at 1, 2, and 3 years were observed in both the safety and PP populations among participants who maintained a 25 mg avapritinib

dose at the data cut. Among participants who escalated to 50 mg, further reductions in serum tryptase were observed from the time of escalation, indicating additional benefit for patients meeting the clinical criteria for dose increase.¹

Table 3.22: Change in serum tryptase from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose	All starting doses	25 mg starting dose	All starting doses
Baseline				
N	■	■	■	■
Concentration, median, ng/mL (range)	■	■	■	■
~ 1 year from baseline (C13 D1)				
N	■	■	■	■
Concentration, median, ng/mL (range)	■	■	■	■
Change in concentration from baseline, median, ng/mL (range)	■	■	■	■
Percent change in concentration from baseline, median (range)	■	■	■	■
~ 2 years from baseline (C25D1)				
N	■	■	■	■
Concentration, median, ng/mL (range)	■	■	■	■
Change in concentration from baseline, median,	■	■	■	■

Parameter	ITT population		PP population	
	25 mg starting dose	All starting doses	25 mg starting dose	All starting doses
ng/mL (range)				
Percent change in concentration from baseline, median (range)				
~ 3 years from baseline (C40D1)				
N				
Concentration, median, ng/mL (range)				
Change in concentration from baseline, median, ng/mL (range)				
Percent change in concentration from baseline, median (range)				
Based on Table 25 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; ITT = intention-to-treat; PP = per-protocol				

Table 3.23: Change in *KIT* D816V VAF from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose	All starting doses	25 mg starting dose	All starting doses
Baseline				
N				
<i>KIT</i> D816V VAF, median (range)				
~ 1 year from baseline (C13 D1)				

Parameter	ITT population		PP population	
	25 mg starting dose	All starting doses	25 mg starting dose	All starting doses
N	■	■	■	■
<i>KIT</i> D816V VAF, median (range)	■	■	■	■
Change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
~ 2 years from baseline (C25D1)				
N	■	■	■	■
<i>KIT</i> D816V VAF, median (range)	■	■	■	■
Change in <i>KIT</i> D816V VAF from baseline, median (range)	■	■	■	■
Percent change in <i>KIT</i> D816V VAF from baseline	■	■	■	■

Parameter	ITT population		PP population	
	25 mg starting dose	All starting doses	25 mg starting dose	All starting doses
, median (range)				
~ 3 years from baseline (C40D1)				
N				
<i>KIT</i> D816V VAF, median (range)				
Change in <i>KIT</i> D816V VAF from baseline, median (range)				
Percent change in <i>KIT</i> D816V VAF from baseline, median (range)				
Based on Table 26 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; ITT = intention-to-treat; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PP = per-protocol; VAF = variant allele frequency				

3.2.7.4 Health-related quality of life

3.2.7.4.1 MC-QoL at 1, 2 and 3 years avapritinib treatment

The company reported that, in the ITT population, mean MC-QoL total scores decreased by [REDACTED] points after 1 year of avapritinib treatment, with reductions maintained at 2 years ([REDACTED] points) and 3 years ([REDACTED] points). Similar reductions were observed in the PP population.¹ Further details can be found in Table 3.24. The company also stated that participants who maintained a 25 mg dose of avapritinib in both the safety and PP populations experienced comparable reductions in mean MC-QoL total scores from baseline at 1, 2, and 3 years of follow-up compared with the overall populations.¹

Table 3.24: Change in MC-QoL total score from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose (N=)	All starting doses (N=)	25 mg starting dose (N=)	All starting doses (N=)
Baseline				
N				
MC-QoL total score, mean (SD)				
~ 1 year from baseline (C13 D1)				
N				
MC-QoL total score, mean (SD)				
Change in MC-QoL total score from baseline, mean (SD)				
Percent change in MC-QoL total score from baseline, mean (SD)				
~ 2 years from baseline (C25D1)				
N				
MC-QoL score, mean (SD)				
Change in MC-QoL total score from baseline, mean (SD)				
Percent change in MC-QoL total score from baseline, mean (SD)				
~ 3 years from baseline (C40D1)				
N				
MC-QoL score, mean (SD)				
Change in MC-QoL total score from baseline, mean (SD)				
Percent change in MC-QoL total score from baseline, mean (SD)				
Based on Table 27 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; ITT = intention-to-treat; MC-QoL = Mastocytosis Quality of Life; PP = per-protocol; SD = standard deviation				

3.2.7.4.2 EQ-5D-5L at 1, 2 and 3 years

The company reported increases in mean EQ-5D-5L scores from baseline at 1 year (), 2 years (), and 3 years () of avapritinib treatment in the ITT population, suggesting sustained improvements in HRQoL. Similar improvements were observed in the PP population. The company also stated that these improvements were consistent regardless of participants' starting dose or whether a 25 mg dose was maintained at the time of data cut-off (DCO), across both the safety and PP populations.¹ Further details can be found in Table 3.25.

Table 3.25: Change in EQ-5D-5L scores from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose (N=■)	All starting doses (N=■)	25 mg starting dose (N=■)	All starting doses (N=■)
Baseline				
N	■	■	■	■
EQ-5D-5L score, mean (SD)	■	■	■	■
~ 1 year from baseline (C13 D1)				
N	■	■	■	■
EQ-5D-5L score, mean (SD)	■	■	■	■
Change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
Percent change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
~ 2 years from baseline (C25D1)				
N	■	■	■	■
EQ-5D-5L score, mean (SD)	■	■	■	■
Change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
Percent change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
~ 3 years from baseline (C40D1)				
N	■	■	■	■
EQ-5D-5L score, mean (SD)	■	■	■	■
Change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
Percent change in EQ-5D-5L score from baseline, mean (SD)	■	■	■	■
Based on Table 28 of the CS ¹ CS = company submission; CxDx = Cycle x, Day x; EQ-5D-5L = EuroQoL 5-Dimension 5-Level questionnaire; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation				

3.2.7.4.3 SF-12 at 1, 2 and 3 years

The company reported that participants in both the ITT and PP populations demonstrated sustained improvements in HRQoL, as measured by the SF-12 PCS and MCS, over the 3-year treatment period. In the ITT population, mean SF-12 PCS scores increased from baseline by [REDACTED] points at 1 year, [REDACTED] points at 2 years, and [REDACTED] points at 3 years across all starting doses. Corresponding improvements in mean SF-12 MCS scores were [REDACTED], [REDACTED], and [REDACTED] points at 1, 2, and 3 years, respectively. The PP population showed comparable improvements in both PCS and MCS. The company also stated that these improvements were consistent across starting doses of avapritinib and were observed in both analysis populations¹. Further details can be found in Table 3.26.

Table 3.26: Change in SF-12 physical and mental component scores from baseline up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose (N=[REDACTED])	All starting doses (N=[REDACTED])	25 mg starting dose (N=[REDACTED])	All starting doses (N=[REDACTED])
Physical component summary				
Baseline				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SF-12 PCS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~1 year from baseline (C13D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SF-12 PCS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in SF-12 PCS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent change in SF-12 PCS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~2 years from baseline (C25D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SF-12 PCS, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in SF-12 PCS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Percent change in SF-12 PCS from baseline, mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
~3 years from baseline (C40D1)				
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Parameter	ITT population		PP population	
	25 mg starting dose (N=■)	All starting doses (N=■)	25 mg starting dose (N=■)	All starting doses (N=■)
SF-12 PCS, mean (SD)	■	■	■	■
Change in SF-12 PCS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 PCS from baseline, mean (SD)	■	■	■	■
Mental component summary				
Baseline				
N	■	■	■	■
SF-12 MCS, mean (SD)	■	■	■	■
~1 year from baseline (C13D1)				
N	■	■	■	■
SF-12 MCS, mean (SD)	■	■	■	■
Change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
~2 years from baseline (C25D1)				
N	■	■	■	■
SF-12 MCS, mean (SD)	■	■	■	■
Change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
~3 years from baseline (C40D1)				
N	■	■	■	■
SF-12 MCS, mean (SD)	■	■	■	■

Parameter	ITT population		PP population	
	25 mg starting dose (N=■)	All starting doses (N=■)	25 mg starting dose (N=■)	All starting doses (N=■)
Change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
Percent change in SF-12 MCS from baseline, mean (SD)	■	■	■	■
Based on Table 29 of the CS ¹ C = Cycle; CS = company submission; D = Day; ITT = intention-to-treat; MCS = Mental Component Summary; PCS = Physical Component Summary; PP = per-protocol; SD = standard deviation; SF-12 = 12-Item Short Form Health Survey Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.				

3.2.7.4.4 PGIS and PGIC at 1, 2 and 3 years

The company reported mean PGIS scores decreased consistently from baseline over 3 years of avapritinib treatment in the ITT population, suggesting sustained reductions in symptom severity. Across all starting doses, mean PGIS scores decreased by ■ points at 1, 2, and 3 years. Similar reductions were observed in the PP population. The company also stated that, consistent with the PGIS findings, participants in both the ITT and PP populations reported meaningful improvements in symptom severity while on treatment.¹

According to the company, mean PGIC scores in the ITT population were approximately ■ at 1 year, ■ at 2 years, and ■ at 3 years post-baseline, with comparable results in the PP population. The company stated that improvements in PGIS and PGIC were consistent across starting doses and were maintained in both analysis populations over the 3-year treatment period¹. Further details can be found in Table 3.27.

Table 3.27: PGIS summary and change from baseline (time of avapritinib initiation) in PGIS up to 3 years avapritinib (PIONEER Part 3)

Parameter	ITT population		PP population	
	25 mg starting dose (N=■)	All starting doses (N=■)	25 mg starting dose (N=■)	All starting doses (N=■)
PGIS				
Baseline				
N	■	■	■	■
PGIS score, mean (SD)	■	■	■	■
~1 year from baseline (C13D1)				
N	■	■	■	■
PGIS score, mean (SD)	■	■	■	■
Change in PGIS score from baseline, mean (SD)	■	■	■	■
~2 years from baseline (C25D1)				

Parameter	ITT population		PP population	
	25 mg starting dose (N=■)	All starting doses (N=■)	25 mg starting dose (N=■)	All starting doses (N=■)
N	■	■	■	■
PGIS score, mean (SD)	■	■	■	■
Change in PGIS score from baseline, mean (SD)	■	■	■	■
~3 years from baseline (C40D1)				
N	■	■	■	■
PGIS score, mean (SD)	■	■	■	■
Change in PGIS score from baseline, mean (SD)	■	■	■	■
PGIC (7-point scale)				
~1 year from baseline (C13D1)				
N	■	■	■	■
PGIC score, mean (SD)	■	■	■	■
~2 years from baseline (C25D1)				
N	■	■	■	■
PGIC score, mean (SD)	■	■	■	■
~3 years from baseline (C40D1)				
N	■	■	■	■
PGIC score, mean (SD)	■	■	■	■
Based on Table 30 of the CS ¹ C = Cycle; CS = company submission; D = Day; ITT = intention-to-treat; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Symptom; PP = per-protocol; SD = standard deviation Note: Participants who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The PGIS scale ranges from 0 (none) to 4 (very severe). The PGIC scale ranges from 1 (very much worse) to 7 (very much better), with a score of 4 indicating no change and 5 indicating moderately better.				

3.2.7.5 Symptom-directed therapy medication usage alongside avapritinib at 33 months

The company reported that¹ “At baseline, ■ of participants in the PP population were using at least one concomitant SDT therapy to manage ISM symptoms, including IgE antibodies, corticosteroids, cromolyn sodium, histamine H1 and H2 antihistamines, leukotriene inhibitors and proton-pump inhibitors. Notably, ■ of participants were receiving ≥4 SDT therapies at baseline. Long-term avapritinib treatment markedly reduced participants' use of supplementary SDT therapies.

At 33 months (in participants who reached C37D1 or discontinued before C37D1), ■ of participants (all starting doses) experienced an improvement in SDT use (change in dose or schedule) in at least one class of therapy. Among participants with improved SDT use, ■ improved in one class, ■ in two classes, ■ in three classes and ■ in four classes. The most commonly improved SDT therapy classes were H1 antihistamines (■), H2 antihistamines (■) and cromolyn sodium (■). Further details are provided in Table 3.28.

Table 3.28: Change from baseline (time of avapritinib initiation) in SDT use in the PP population at 33 months avapritinib (PIONEER Part 3)

Parameter	25 mg starting dose (N=)	All starting doses (N=)
Baseline		
Participants with SDT use		
At least one therapy, n (%)		
Anti-IgE antibody, n (%)		
Corticosteroids, n (%)		
Cromolyn sodium, n (%)		
H1 antihistamines, n (%)		
H2 antihistamines, n (%)		
Leukotriene inhibitors, n (%)		
Proton-pump inhibitors, n (%)		
Other, n (%)		
Number of classes of SDT used		
One class, n (%)		
Two classes, n (%)		
Three classes, n (%)		
≥Four classes, n (%)		
C37D1*		
Number of classes improved		
At least one class, n (%)		
One class, n (%)		
H1 antihistamines, n (%)		
H2 antihistamines, n (%)		
Cromolyn sodium, n (%)		
Anti-IgE antibody, n (%)		
Other individual classes, n (%)		
Two classes, n (%)		
Three classes, n (%)		
Four classes, n (%)		
Based on Table 31 of the CS ¹ C = Cycle; CS = company submission; D = Day; DCO = data cut-off; H1 = histamine H1 receptor; H2 = histamine H2 receptor; IgE = immunoglobulin E; PP = per-protocol; SDT = symptom-directed therapy Note: * Includes participants who had reached C37D1 or discontinued before C37D1 as of the 21 February 2025 DCO. Participants who initiated avapritinib at 50 mg or 100 mg in Part 1 continued treatment at 25 mg daily at the start of Part 3.		

3.2.7.6 Bone mineral density after 2 years of avapritinib treatment

The company reported that¹ “Exploratory bone health assessments revealed high prevalence of bone-related comorbidities, with osteopenia in 48 patients (19%) and osteoporosis in 56 patients (22%) amongst 251 enrolled participants. In a single-site cohort of 13 patients with serial dual-energy X-ray absorptiometry measurements, mean bone mineral density increases of $4.79 \pm 4.78\%$ at the lumbar

spine and $3.59 \pm 5.58\%$ at the femoral neck were observed after 2 years of avapritinib treatment. At baseline, 8 patients had osteopenia (T-score between -2.5 and -1) and 2 had osteoporosis (T-score ≤ -2.5)”.

EAG comment: In Part 3, the company reported sustained improvements in ISM-related symptoms, objective measures of mast cell burden, and HRQoL over up to 3 years of avapritinib treatment, with findings reported to be consistent across starting doses and analysis populations (ITT and PP). The EAG notes that these results are aligned with the overall trial findings and suggest durability of treatment benefit.

There also seemed to have been a substantial decrease in the use of SDT, which appeared to continue the trend observed in Part 2 at 24 weeks up to 33 months.

The EAG noticed that [REDACTED] participants underwent dose escalation to 50 mg in Part 3 of PIONEER, [REDACTED] of whom started on 25 mg, and requested clarification as to what the starting dose was of those who did not start on 25 mg. The company responded that they were 50 mg ([REDACTED]), and 100 mg ([REDACTED]), and explained that all patients were reduced to 25 mg for Part 3.⁵ Given that 50 mg is not included in the marketing authorisation, and NICE cannot make a decision outside of the marketing authorisation, the EAG asked that company present the results for Part 3 excluding patients who experienced dose escalation, which the company provided. They are not reproduced here for brevity and because they were all very similar to those for the full ITT and PP population, which are reported above. Of course, this lack of difference between those who did not escalate, and all patients does not imply that those who did escalate would have had poorer outcomes had they not. This might affect the generalisability of the PIONEER trial, albeit by a modest amount, and is therefore included as part of the Key Issue regarding whether dose escalation would occur in UK clinical practice (see Section 2.1).

The EAG noted that two patients randomised to avapritinib did not receive any SDT and that 16 patients received only one SDT at baseline, despite the eligibility criterion requiring ≥ 2 SDTs. The EAG therefore requested clarification on how these patients met the eligibility criteria and asked for data on changes from baseline in SDT use for the placebo arm of PIONEER. The company responded that all patients enrolled in PIONEER (avapritinib and placebo) had received at least two current or prior SDT medications, in line with the eligibility criteria, noting that ≥ 2 SDTs may have been administered prior to baseline assessment. The EAG consider that this explains the figures reported in Table 3.28.

3.2.8 Subgroup analyses of PIONEER trial

The company reported subgroup analyses for the primary and key secondary efficacy endpoints, as well as for adverse events (AEs), based on age, sex, country, baseline ISM status, ECOG PS, baseline serum tryptase level, and prior TKI therapy. Overall, the efficacy subgroup analyses suggested that avapritinib provided benefits across most subgroups, as reflected by reductions in ISM-SAF TSS and objective measures of mast cell burden at 24 weeks.¹

The company reported small, non-statistically significant numerical differences in ISM-SAF TSS reduction were observed by sex, with mean differences (MDs) between avapritinib and placebo of [REDACTED] points in males and [REDACTED] points in females; however, the small male sample size (placebo n=17; avapritinib n=[REDACTED]) limits interpretation. Baseline serum tryptase level also appeared to influence treatment response, with a MD of [REDACTED] points in patients with <20 ng/mL compared with [REDACTED] points in those with ≥ 20 ng/mL. The subgroup with baseline serum tryptase <20 ng/mL was small (placebo n=14; avapritinib n=[REDACTED]).¹

The company further stated that for safety, the AE profile of avapritinib was generally consistent across subgroups, with no new safety signals identified, including in Part 3 and the overall analyses with longer follow-up¹.

EAG comment: Overall, the subgroup results do not raise concerns regarding the generalisability of the trial findings. There are subgroups where there might be a concern, although inference is limited due to small sample sizes of males and participants with baseline serum tryptase <20 ng/mL.

3.2.9 Safety results of PIONEER trial

3.2.9.1 Part 1 safety results

The company stated that the mean treatment duration was similar across groups, ranging from [REDACTED] weeks in Part 1, and that the overall incidence of AEs was comparable between treatment groups. [REDACTED] occurred in the 50 mg avapritinib group due to an AE of delirium. AEs leading to dose modifications were reported in [REDACTED] of placebo participants and in [REDACTED] of participants receiving 25 mg, 50 mg, and 100 mg avapritinib, respectively.¹

The company reported that “The most common AEs (>15%) in either group (placebo; avapritinib all doses) [REDACTED] were noted only in avapritinib-treated participants”.¹

The company further stated that no intracranial bleeding events were reported. Cognitive effect AEs included cognitive disorder and memory impairment, reported in [REDACTED] each in the 25 mg and 100 mg groups, respectively, and a serious adverse event (SAE) of delirium in [REDACTED] in the 50 mg group. Most cognitive events were non-serious and Grade 1 or 2; [REDACTED] was Grade 3 and led to treatment discontinuation. No cognitive effect events were reported in the placebo group.¹

The company concluded that avapritinib was generally well tolerated across all doses, with the 25 mg dose showing a safety profile similar to placebo and no Grade ≥3 AEs, SAEs, dose modifications, or discontinuations. No deaths or clinically significant trends in laboratory parameters, vital signs, electrocardiograms (ECGs), or physical examinations were reported.¹ Further details can be found in Table 3.29.

Table 3.29: Summary of AEs (PIONEER Part 1 ITT population)

Parameter	Placebo (N=[REDACTED]) n (%)	Avapritinib 25 mg (N=[REDACTED]) n (%)	Avapritinib 50 mg (N=[REDACTED]) n (%)	Avapritinib 100 mg (N=[REDACTED]) (%)
Any AEs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Related AEs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Serious AEs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Grade 3 or higher AEs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AEs leading to dose modifications	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AEs leading to study drug discontinuation	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Deaths	■	■	■	■
Based on Table 32 of the CS ¹ AE = adverse event; CS = company submission; ITT = intention-to-treat				

3.2.9.2 Part 2 safety results

The company reported that 141 participants received avapritinib 25 mg and 71 received placebo in Part 2. The mean (SD) treatment duration was 5.46 (0.726) months in the avapritinib group and 5.43 (0.806) months in the placebo group. The median relative dose intensity for avapritinib was 100% (range: 83%-101%)¹.

The safety profile of avapritinib 25 mg QD was reported to be similar to that of placebo. At least one AE occurred in 90.8% of participants in the avapritinib group and 93.0% in the placebo group, while drug-related AEs were reported in 54.6% and 45.1% of participants, respectively. SAEs were less frequent with avapritinib (5.0%) than placebo (11.3%), with no drug-related SAEs in either group.¹

The company stated that the most common AEs ($\geq 10\%$) were headache, nausea, Coronavirus disease 2019 (COVID-19), dizziness, and diarrhoea. Facial oedema was the only AE with a $>5\%$ higher incidence in the avapritinib group (7.1% versus 1.4%). Overall, oedema events were more frequent with avapritinib than placebo (■ versus ■), were predominantly Grade 1 or 2 (mostly Grade 1), and no AEs were Grade ≥ 3 .¹

The company further stated that cognitive effect events were infrequent and occurred in a slightly lower proportion of participants receiving avapritinib than placebo (2.8% versus 4.2%), with memory impairment being the most commonly reported event (■). No clinically relevant between-group differences were reported for haematology parameters, and no deaths occurred during Part 2 of the study.¹ Further details can be found in Table 3.30.

Table 3.30: Overview of safety results (PIONEER Part 2 ITT population)

Parameter	Avapritinib 25 mg (N=141) n (%)	Placebo (N=71) n (%)
General safety summary		
Participants with at least one AE	128 (90.8)	66 (93.0)
AE-related to study drug	77 (54.6)	32 (45.1)
SAE	7 (5.0)	8 (11.3)
SAE related to study drug	0	0
Grade 1 AE	48 (34.0)	15 (21.1)
Grade 2 AE	50 (35.5)	36 (50.7)
Grade ≥ 3 AE	30 (21.3)	15 (21.1)
Grade ≥ 3 AE-related to study drug	3 (2.1)	2 (2.8)
AE leading to interruption of study drug	12 (8.5)	9 (12.7)
AE leading to dose reduction of study drug	2 (1.4)	1 (1.4)
AE leading to permanent discontinuation	3 (2.1)	1 (1.4)
Death	0	0
Common AEs ($\geq 10\%$ in either group)		
Headache	27 (19.1)	14 (19.7)
Nausea	18 (12.8)	12 (16.9)

Parameter	Avapritinib 25 mg (N=141) n (%)	Placebo (N=71) n (%)
COVID-19	17 (12.1)	8 (11.3)
Dizziness	16 (11.3)	6 (8.5)
Diarrhoea	15 (10.6)	8 (11.3)
Oedema events		
Participants with at least one AE of oedema	36 (25.5)	8 (11.3)
Oedema peripheral	12 (8.5)	3 (4.2)
Face oedema	10 (7.1)	1 (1.4)
Periorbital oedema	9 (6.4)	2 (2.8)
Cognitive effect events		
Participants with at least one AE of cognitive effect	4 (2.8)	3 (4.2)
Memory impairment	2 (1.4)	1 (1.4)
Amnesia	1 (0.7)	0
Mood altered	1 (0.7)	0
Mental impairment	0	1 (1.4)
Mental status changes	0	1 (1.4)
Based on Table 33 of the CS ¹ AE = adverse event; CS = company submission; COVID-19 = Coronavirus disease 2019; ITT = intention-to-treat; SAE = serious adverse event		

3.2.9.3 Part 3 OLE safety results

The company reported that Part 3 included participants who completed Parts 1 or 2 and rolled over into the OLE. In the ITT population, the mean duration of treatment was [REDACTED] months for participants who initiated avapritinib at a 25 mg starting dose and [REDACTED] months for those who initiated avapritinib at any starting dose. The corresponding median treatment durations were 40.0 months (range: 0.7–67.2) and 40.1 months (range: 0.2–67.2), respectively. Most participants received treatment for ≥ 6 months ([REDACTED]), ≥ 12 months ([REDACTED]), ≥ 24 months ([REDACTED]), and ≥ 36 months ([REDACTED]), respectively.

The company stated that, based on the latest data DCO for Part 3, AE profiles were comparable between participants who initiated avapritinib at 25 mg ([REDACTED]) and those who initiated treatment at any dose ([REDACTED]), as well as between the overall ITT safety population and participants who maintained a 25 mg dose at the time of the DCO. No new safety concerns were observed among participants who dose-escalated to 50 mg. Further details are provided in Table 3.31.

The company also reported that avapritinib demonstrated a consistent safety profile across analysis populations, with the most frequently reported AEs ($\geq 10\%$ of the safety population) including [REDACTED]. No new safety concerns were identified at the latest DCO compared with earlier time points. Further details can be found in Tables 3.32.

According to the company, across Part 3 analysis populations, the proportion of participants experiencing SAEs was similar between the 25 mg starting dose group [REDACTED] and the starting doses

group [REDACTED]. Although anaphylactic reactions were reported as SAEs ([REDACTED] these events are a recognised clinical manifestation of ISM. As shown in Table 3.33, only a small number of SAEs were considered related to avapritinib.

Table 3.31: Summary of AEs in PIONEER safety population at DCO

Participants with at least one event, n (%)	25 mg starting dose (N=226)	All starting doses (N=246)
Any AE	[REDACTED]	[REDACTED]
AE-related to study drug	[REDACTED]	[REDACTED]
SAE	[REDACTED]	[REDACTED]
SAE related to study drug	[REDACTED]	[REDACTED]
Grade ≥ 3 AE	[REDACTED]	[REDACTED]
Grade ≥ 3 AE-related to study drug	[REDACTED]	[REDACTED]
AE leading to interruption of study drug	[REDACTED]	[REDACTED]
AE-related to study drug leading to interruption of study drug	[REDACTED]	[REDACTED]
AE leading to reduction of study drug	[REDACTED]	[REDACTED]
AE-related to study drug leading to reduction of study drug	[REDACTED]	[REDACTED]
AE leading to permanent discontinuation of study drug	[REDACTED]	[REDACTED]
AE-related to study drug leading to permanent discontinuation of study drug	[REDACTED]	[REDACTED]
AE leading to death	[REDACTED]	[REDACTED]
Based on Table 34 of the CS ¹ AE = adverse event; CS = company submission; DCO = data cut-off; SAE = serious adverse event		

Table 3.32: AEs that occurred in $\geq 10\%$ of the PIONEER safety population (avapritinib, all starting doses) at DCO

Patients with at least one event by preferred term, n (%)	Avapritinib, 25 mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25 mg dose maintained (N=175)	Avapritinib, 25 mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
[REDACTED]	159 (98.8)	172 (98.3)	224 (99.1)	243 (98.8)
[REDACTED]	75 (46.6)	79 (45.1)	115 (50.9)	123 (50.0)
[REDACTED]	34 (21.1)	40 (22.9)	54 (23.9)	63 (25.6)
[REDACTED]	38 (23.6)	43 (24.6)	54 (23.9)	60 (24.4)
[REDACTED]	31 (19.3)	40 (22.9)	49 (21.7)	60 (24.4)
[REDACTED]	31 (19.3)	36 (20.6)	52 (23.0)	57 (23.2)
[REDACTED]	25 (15.5)	28 (16.0)	43 (19.0)	47 (19.1)
[REDACTED]	24 (14.9)	27 (15.4)	41 (18.1)	46 (18.7)
[REDACTED]	30 (18.6)	34 (19.4)	40 (17.7)	45 (18.3)

Patients with at least one event by preferred term, n (%)	Avapritinib, 25 mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25 mg dose maintained (N=175)	Avapritinib, 25 mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
■	29 (18.0)	32 (18.3)	35 (15.5)	42 (17.1)
■	22 (13.7)	23 (13.1)	35 (15.5)	37 (15.0)
■	21 (13.0)	21 (12.0)	32 (14.2)	36 (14.6)
■	26 (16.1)	27 (15.4)	34 (15.0)	35 (14.2)
■	15 (9.3)	19 (10.9)	27 (11.9)	34 (13.8)
■	23 (14.3)	25 (14.3)	31 (13.7)	34 (13.8)
■	14 (8.7)	17 (9.7)	30 (13.3)	33 (13.4)
■	18 (11.2)	22 (12.6)	27 (11.9)	32 (13.0)
■	18 (11.2)	22 (12.6)	27 (11.9)	31 (12.6)
■	17 (10.6)	19 (10.9)	27 (11.9)	30 (12.2)
■	15 (9.3)	17 (9.7)	27 (11.9)	29 (11.8)
■	18 (11.2)	20 (11.4)	25 (11.1)	28 (11.4)
■	15 (9.3)	16 (9.1)	24 (10.6)	27 (11.0)
■	17 (10.6)	18 (10.3)	25 (11.1)	26 (10.6)
■	13 (8.1)	13 (7.4)	25 (11.1)	26 (10.6)
Based on Table 35 of the CS ¹ AE = adverse event; ALP = alkaline phosphatase; COVID-19 = Coronavirus disease 2019; CS = company submission; DCO = data cut-off Note: Patients who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.				

Table 3.33: SAEs that occurred in ≥ 2 patients in the PIONEER safety population (avapritinib, all starting doses) at DCO

Patients with at least one event by preferred term, n (%)	Avapritinib, 25 mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25 mg dose maintained (N=175)	Avapritinib, 25 mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
■	30 (18.6)	34 (19.4)	47 (20.8)	54 (22.0)
■	3 (1.9)	4 (2.3)	7 (3.1)	8 (3.3)
■	1 (0.6)	2 (1.1)	3 (1.3)	4 (1.6)
■	2 (1.2)	2 (1.1)	3 (1.3)	3 (1.2)
■	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)
■	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
■	0	1 (0.6)	1 (0.4)	2 (0.8)
■	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)

Patients with at least one event by preferred term, n (%)	Avapritinib, 25 mg starting dose and dose maintained (N=161)	Avapritinib, all starting doses and 25 mg dose maintained (N=175)	Avapritinib, 25 mg starting dose (N=226)	Avapritinib, all starting doses (N=246)
██████████	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.8)
██████████████████	0	1 (0.6)	1 (0.4)	2 (0.8)
██████████████████	0	0	2 (0.9)	2 (0.8)
██████████████	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
██████████████████	2 (1.2)	2 (1.1)	2 (0.9)	2 (0.8)
██████████████	0	0	2 (0.9)	2 (0.8)
██████████	1 (0.6)	2 (1.1)	1 (0.4)	2 (0.8)
Based on Table 36 of the CS ¹ COVID-19 = Coronavirus disease 2019; CS = company submission; DCO = data cut-off; SAE = serious adverse event Note: Patients who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3.				

EAG comment: Overall, the safety results presented by the company appear broadly consistent across the three study parts (Parts 1, 2 and 3) and across dose groups. In Part 1, █████ SAE of delirium was reported in the avapritinib 50 mg group, which limits the interpretation of dose-related safety due to the small number of events. In Part 2, a higher incidence of oedema was observed in the avapritinib 25 mg group compared with placebo; however, the clinical relevance of this difference is unclear, and no formal statistical comparisons were presented. In Part 3, the incidence of AEs was similar between participants initiating avapritinib at 25 mg and those initiating at all starting doses, suggesting no clear dose-dependent safety signal.

The company also reported SAEs of ████████████████████ (ranging from █████ to █████%) and stated that anaphylaxis is a common clinical manifestation of ISM. The EAG considers this attribution to be plausible given the disease context; however, limited detail was provided on the assessment of causality, and uncertainty remains regarding the relationship between treatment and these events. Overall, while no major safety concerns were identified, the lack of comparative analyses restrict the robustness of the safety conclusions.

The EAG requested that the company provide more detailed data on anaphylaxis in the PIONEER trial, including the number of patients and events, the timing of events (by study part and week), and an estimate of the treatment effect (avapritinib versus placebo). The company subsequently provided these additional data⁵ *“During the course of PIONEER Part 2 (randomised avapritinib vs placebo for 24 weeks), the number of anaphylaxis events treated with epinephrine were recorded during screening (baseline) and throughout the study (24 weeks post-baseline). At baseline, █████ patients in the 25 mg avapritinib group and none in the placebo group had anaphylaxis that required epinephrine treatment. Post-baseline, █████ patients in the 25 mg avapritinib group and 3 (4.2%) in the placebo group had anaphylaxis that required epinephrine treatment.*

It should be noted that the above results are for PIONEER Part 2 up to 24 weeks only, and the timing of the anaphylactic events was not captured for all patients across the multiple clinical trial sites.

Exploratory analyses revealed a reduction of anaphylaxis frequency with avapritinib treatment, [REDACTED] of patients who had baseline anaphylaxis (N=[REDACTED]) experienced no post-baseline events during the 24-week treatment period, compared to all placebo patients (N=[REDACTED]) developing anaphylaxis only during treatment. With this small sample size of patients/anaphylactic events, it is difficult to infer treatment effect highlighting the need for further study in a real-world setting over longer periods of time”.

In conclusion, it does appear that avapritinib might reduce the rate of anaphylaxis, and the EAG agree that this is very uncertain because of low rate of events.

3.2.10 Treatment discontinuation

The company reported that the most common reasons for discontinuation across Parts 1, 2, and 3 were withdrawal of consent ([REDACTED] in ITT population, [REDACTED] in PP population), followed by AEs ([REDACTED] in ITT population, [REDACTED] in PP population), and other reasons including progressive disease, investigator decision, non-compliance, pregnancy, lost to follow-up, and death unrelated to study drug.¹

EAG comment: The EAG requested more detailed information on avapritinib discontinuation, and in response the company provided a Table (see Table 3.34).⁵

Table 3.34: Summary of reasons for discontinuation of avapritinib treatment in PIONEER study Parts 1, 2 and 3

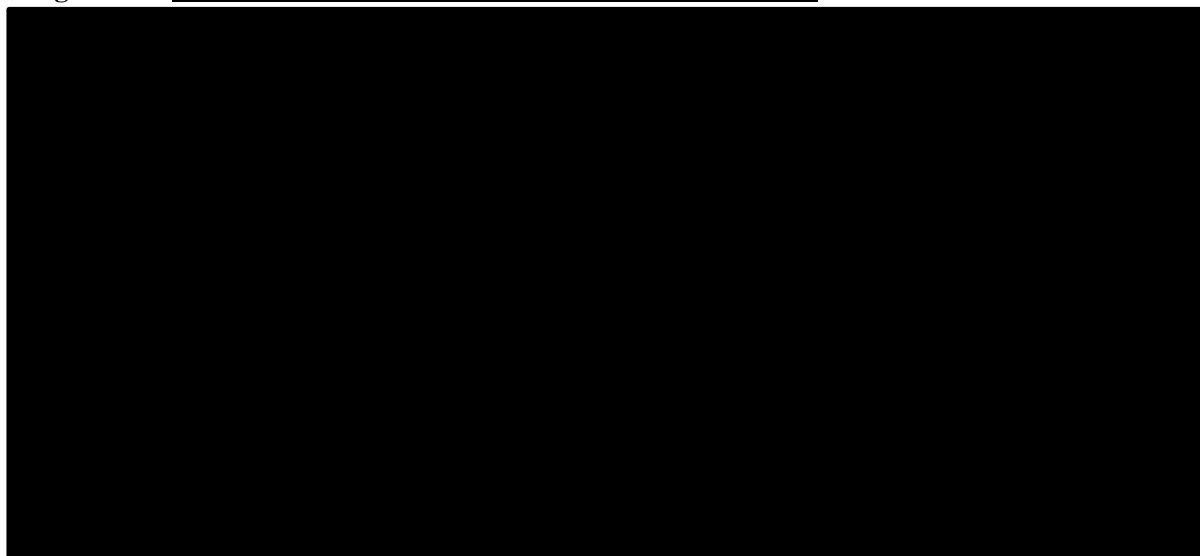
Reason for discontinuation	Number of participants	Duration of avapritinib treatment before discontinuation, mean (range) months
Withdrawal by subject	[REDACTED]	[REDACTED]
AE	[REDACTED]	[REDACTED]
Physician decision	[REDACTED]	[REDACTED]
Progressive disease	[REDACTED]	[REDACTED]
Non-compliance	[REDACTED]	[REDACTED]
Lost to follow-up	[REDACTED]	[REDACTED]
Death	[REDACTED]	[REDACTED]
Pregnancy	[REDACTED]	[REDACTED]
Other	[REDACTED]	[REDACTED]
Total discontinued	[REDACTED]	
Source: Table 15, clarification letter response ⁵ AE = adverse event		

From a Kaplan-Meier (K-M) analysis of the entire follow-up including Part 3, the median time to discontinuation (TTD) for the overall population was [REDACTED] months ([REDACTED] CI: [REDACTED]), which varied by treatment group, although it was similar for the largest group of those who started and remained on 25mg i.e. [REDACTED].

The probability of remaining on treatment was:

- 12 months: [REDACTED] probability of remaining on treatment
- 24 months: [REDACTED] probability of remaining on treatment
- 36 months: [REDACTED] probability of remaining on treatment
- 48 Months: [REDACTED] probability of remaining on treatment
- 60 months: [REDACTED] probability of remaining on treatment

The K-M plot is shown in Figure 3.8.

Figure 3.8:

Source: Figure 1, response to clarification letter⁵

K-M = Kaplan-Meier; TTD = time to treatment discontinuation

For a discussion of the relevance of these data, please see Section 4.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

There was no indirect treatment comparison (ITC) in the CS.¹

EAG comment: The EAG noted that some comparator treatments were not received by patients in PIONEER, and so the relative effectiveness of avapritinib as add-on instead of them cannot be estimated using PIONEER. Therefore, the EAG requested an ITC, if feasible, for all such treatments, to which the company responded that an ITC was not appropriate for several reasons.⁵ Having examined the arguments by the company and the EAG clinical expert evidence (see Section 2.3), the EAG considers that most or all treatments that avapritinib could be added to in UK clinical practice could be regarded as SDT. These are already included in the PIONEER trial, and with percentage use that has been compared to UK clinical practice by both the company and the EAG (see Section 3.2.4).

The exceptions that might be used in clinical practice are the TKIs, although one clinical expert stated these are for advanced disease.

In conclusion, the EAG agree with the company that, assuming the comparator should be SDT, the PIONEER trial is probably the best source of evidence, albeit with questionable generalisability, and that no ITC is required. If, on the other hand, some patients who might be eligible for avapritinib get non-SDT e.g. a TKI then some kind of ITC would be warranted, and its feasibility formally assessed.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

There was no ITC in the CS.¹

EAG comment: Please refer to the EAG comment in Section 3.3.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None carried out.

3.6 Conclusions of the clinical effectiveness section

The CS and Appendix B^{1, 10} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the use of avapritinib for treating inadequately controlled moderate to severe ISM. Searches were conducted in July 2025, and were transparent and reproducible, and a good range of bibliographic databases, conference proceedings, trials registers and HTA resources were searched. Overall, the EAG has no concerns about the literature searches conducted.

The main source of evidence for the effectiveness of avapritinib as add-on to standard care versus standard care is an RCT, the PIONEER trial Part 2, where avapritinib 25 mg + SDT was compared to placebo + SDT over the double-blind period of 24 weeks. Additional evidence is in the form of PIONEER Part 1, a dose escalation study, where it was determined that 25 mg was the dose to use in Part 2, and Part 3, which provided longer term follow-up (up to 3 years) of 25 mg treatment.

The EAG noted that there are discrepancies between PIONEER and the clinical experts in the percentage use of each kind of SDT (H1-blockers, H2-blocker (cimetidine), PPI (omeprazole), leukotriene inhibitor (montelukast), corticosteroid (prednisolone), cromolyn sodium, omalizumab and loperamide). This is therefore regarded as a Key Issue, although the difference that this makes is difficult to estimate, and also depends on what is actually used in clinical practice, which also varies between the various clinical experts (see Section 2.3).

Overall, there were better outcomes with avapritinib 25 mg than placebo, including statistically significant differences in change in overall symptom score (ISM-SAF TSS), and proportion achieving both $\geq 30\%$ $\geq 50\%$ reduction in TSS. However, treatment effects were not observed consistently across all ISM-SAF symptom domains, with improvements primarily driven by the skin domain, suggesting potential heterogeneity of effect across symptoms. This might be a concern if patients become eligible for avapritinib because their symptoms are predominantly not skin-related or those of the skin not the most severe. Indeed, the baseline characteristics of Part 2 of PIONEER show that a high percentage of patients (about 80%) have symptoms that are not skin-related (see Section 3.2.4), although it is unclear as to the degree of overlap between the various domains. This is therefore regarded as a Key Issue by the EAG.

Twenty-one percent (30/141) of patients receiving avapritinib decreased SDT use versus 13% (9/71) receiving placebo, and 3% (4/141) of patients in the avapritinib group completely discontinued SDT, implying that patients treated with avapritinib were more likely to reduce or discontinue SDT.

In Part 3, the company reported sustained improvements in ISM-related symptoms, objective measures of mast cell burden, and HRQoL over up to 3 years of avapritinib treatment, which the EAG notes suggest durability of treatment benefit. There also seemed to have been a substantial decrease in the use of SDT, which appeared to continue the trend observed in Part 2 at 24 weeks up to 33 months. The EAG noticed that ■ participants underwent dose escalation to 50 mg in Part 3 of PIONEER. Given that 50 mg is not included in the marketing authorisation, and NICE cannot make a decision outside of the marketing authorisation, the EAG asked that company present the results for Part 3 excluding patients who experienced dose escalation, which the company provided, and which showed little difference to the results including all patients. However, those who did escalate might have had poorer

outcomes had they not, which this might affect the generalisability of the PIONEER trial, albeit by a modest amount, and is therefore included as part of the Key Issue regarding whether dose escalation would occur in UK clinical practice (see Section 2.1).

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

4.1.1 Searches performed for cost effectiveness section

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of the searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

The following paragraphs contain summaries and critiques of the searches presented in the CS¹ to identify studies on CE, HRQoL and cost and healthcare resource use (HCRU). The evidence-based checklist for the PRESS from Canada's Drug Agency (formerly the CADTH) was used to inform this critique.⁹ The EAG has presented only the major limitations of each search strategy in the report.

EAG comment:

- The CS, Appendix E,¹⁰ provided sufficient details for the EAG to appraise the literature searches for CE studies, Appendix F,¹⁰ sufficient details for the appraisal of the literature searches for HRQoL studies and Appendix G,¹⁰ sufficient details for the appraisal of the literature searches for studies on cost and HCRU.
- All three searches were well constructed, including subject headings. A good range of synonyms was used. It is not clear if the facets for CE, HRQoL and cost and HCRU were validated search filters. However, all three facets included a sufficient number of search terms and the EAG had no concerns.
- In all three searches, a good range of databases were searched from inception on 28 July 2025: MEDLINE (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations), Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Econlit. The Database of Abstracts of Reviews of Effects and the NHS Economic Evaluation Database were searched from inception to the 1st quarter of 2016 when the databases were no longer updated, and the HTA database from inception to the 4th quarter of 2016.
- No date or language limits were applied to the Embase, MEDLINE or Cochrane Library searches, and no publication type or human limits were applied to the Embase or MEDLINE searches.
- The same 22 conference proceedings and 11 HTA websites were searched as for the clinical effectiveness studies. The EAG query whether earlier years could also have been searched for the HTA material. The EAG could not see the date on which these grey literature searches were undertaken. The EAG feels that the number of hits from the grey literature searches before screening should be the figure reported in the PRISMA flowcharts in Figure 8 (Appendix E¹⁰), Figure 9 (Appendix F¹⁰), and Figure 10 (Appendix G¹⁰), to match how the numbers of results from the database searches were reported. All three PRISMA flowcharts record that reference checking was undertaken, but there are no details of this in the Appendices.
- The first sentence of Appendix F¹⁰ reads: "*The following search strategy was used to identify economic evaluations*", but the strategies are designed to find HRQoL studies, so the EAG are not sure if this is a typographical error.

- Appendix G¹⁰ records that the HTA database was searched from inception to the 1st quarter of 2016 after which it was no longer updated, rather than the 4th quarter of 2016, as recorded in Appendix E and Appendix F. The EAG is not easily able to tell when updating of the HTA database stopped, although it may be the 1st quarter of 2018, rather than a date in 2016.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on CE studies, utilities and costs and resource use are presented in the company's Appendix, Tables 31, 40 and 52 respectively.

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify CE studies. One potential question was raised by the company's decision to exclude studies in the advanced SM population, while including SSM, however, this is unlikely to lead to exclusion of relevant CEAs. For HRQoL and cost and resource use, some relevant studies may be missed because of this, but the EAG considers the likely impact to be small. The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Findings of the CE review

The PRISMA flow diagram for the economic model SLR can be found in Figure 8 of Appendix E, and for the HRQoL and cost and resource use in Figures 9 and 10 of Appendix F and G.

No studies were included in the final selection for the health economic model review, 17 were included for the HRQoL review and eight included studies were cost and resource use studies.

4.1.4 Conclusions of the CE review

The CS provides an overview of the included CE, utility and resource use and costs studies, but no specific conclusion was formulated.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent
Perspective on costs	NHS and PSS	Consistent
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent
Synthesis of evidence on health effects	Based on systematic review	Consistent

Element of HTA	Reference case	EAG comment on CS
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Consistent
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Consistent
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent
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	Consistent
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent
CS = company submission; EAG = External Assessment Group; EQ-5L = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALYs = quality-adjusted life years; UK = United Kingdom		

4.2.2 Model structure

A de novo disease activity model was developed in Microsoft Excel to simulate the severity of ISM and progression to SSM and AdvSM. The economic model comprises six mutually exclusive health states (Figure 4.1):

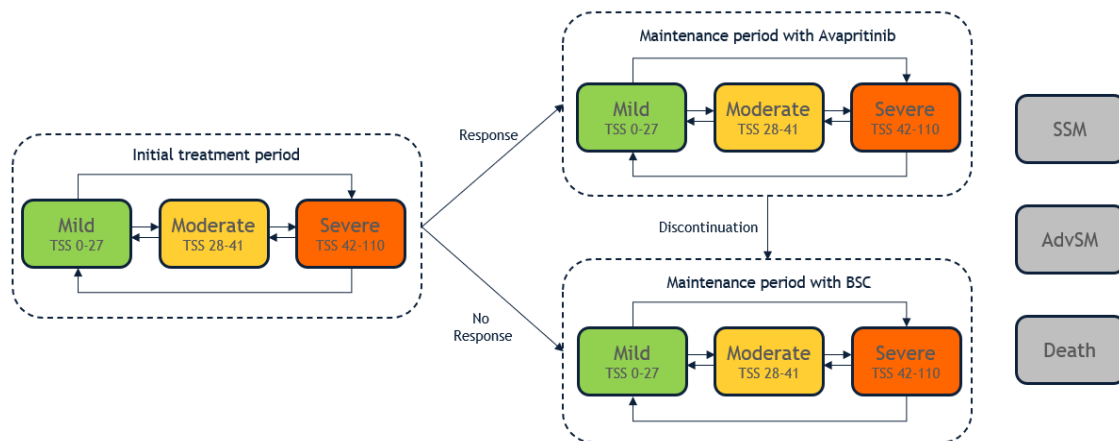
- a) Mild ISM (TSS 0-27)
- b) Moderate ISM (TSS 28-41)
- c) Severe ISM (TSS 42-110)
- d) SSM
- e) AdvSM
- f) Death

Key model assumptions:

- g) Disease-related assumptions
 - ISM severity was defined using TSS categories for mild (TSS 0-27), moderate (TSS 28-41) and severe (TSS 42-110) disease.
 - The distribution of patients entering the economic model was based on their baseline severity in PIONEER.
 - Health state occupancy was directly informed by the PIONEER trial data.
- h) Treatment-related assumptions
 - At the end of a 24-week treatment period, patients on avapritinib were classified as either responders ($\geq 30\%$ TSS improvement) or non-responders ($< 30\%$ TSS improvement).
 - Avapritinib non-responders discontinued avapritinib treatment at 24 weeks, whereas avapritinib responders continue treatment until 7.64 years.
 - SDT treatment was assumed to continue indefinitely.

- The avapritinib treatment effect was modelled directly from observed TSS distributions in the PIONEER trial. Beyond the trial follow-up (252 weeks), patients were assumed to remain in their current health state until discontinuation, after which they transitioned to the SDT health state distribution.
- The SDT treatment effect in the first 24 weeks was modelled directly from observed TSS distributions in the PIONEER trial. Thereafter, patients were assumed to return to their baseline health state distribution.
- No mortality difference was assumed between avapritinib and SDT.

Figure 4.1: Model structure



Retrieved from the company's economic model

AdvSM = advanced systemic mastocytosis; BSC = best supportive care; SSM = smouldering systemic mastocytosis

EAG comment: The main concerns of the EAG relate to: a) the use of ISM-SAF TSS as a measure to score disease severity, b) the use of a symptom-based model structure, and c) inclusion of smouldering systemic mastocytosis (SSM) and advanced systemic mastocytosis (AdvSM) health states.

- a) The EAG questions the appropriateness of the ISM-SAF TSS that was used by the company to distinguish between mild, moderate and severe ISM in its model structure. One EAG clinical expert stated that ISM-SAF TSS is not routinely used in clinical practice in dermatology and argued that it is not an ideal measure outside of the research setting: most patients do not have a great deal of variation in their skin symptoms (likewise for severe gastrointestinal, neurological and musculoskeletal symptoms) from day to day, and very severe symptoms without systemic symptoms should not exclude them from treatment. Another expert consulted by the EAG stated that *"TSS is being increasingly used in clinical practice and adoption would be increased if enable access to better treatments which has not been the case up to this point for ISM"*. In response to the clarification letter, the company stated that ISM-SAF TSS is considered an appropriate and clinically meaningful measure as symptom burden is the primary manifestation of disease severity in patients with ISM and TSS captures the frequency and severity of key symptoms directly affecting patients HRQoL and healthcare utilisation. The company further stated that TSS has been validated by clinicians and that consultation with two UK clinical experts confirmed that the symptom domains captured by TSS align with clinical assessment in National Health Service (NHS) practice. Alternative outcomes for defining ISM disease severity were considered, including biological or disease burden-based measures, but the company noted that none of these were

specific for ISM, nor used in clinical practice. The EAG's clinical expert agrees that measures such as mast cell infiltration and tryptase levels often do not correlate well with symptoms, and further stated that most dermatologists do not regularly use a specific scoring system in clinical practice, with PGIS (score 0-4) being the closest one.

The EAG is concerned that there is a mismatch between the disease severity classification in the company's model structure and disease severity classification in clinical practice, resulting in patients being classified as mild disease in the company's model while these would potentially be treated with avapritinib in UK clinical practice. The EAG considers this a Key Issue.

- b) In its clarification letter, the EAG requested the company to comment on the appropriateness of using a symptom-based model structure to define mild, moderate and severe ISM. The company responded that a symptom-based model structure is consistent with both clinical management of ISM and available evidence. It stated that in UK clinical practice, treatment decisions and HCRU are largely determined by the severity of symptoms and their impact on HRQoL. The company's symptom-based model structure was validated by UK clinical experts and alternative model structures based on biological markers (i.e. mast cell infiltration, serum tryptase levels, or KIT D816V allele burden) were considered less suitable as these are not routinely used in UK clinical practice nor are strongly correlated with symptom burden or long-term changes in HCRU. The EAG's clinical expert agreed that a symptom-based model is most appropriate as mast cell infiltration and tryptase levels often do not correlate well with symptoms. Based on the responses above, the EAG considers the company's symptom-based model structure to be appropriate.
- c) The EAG requested clarification on the SSM and AdvSM health states in the company's model, specifically whether it would be possible in UK clinical practice for ISM patients to progress to these more advanced disease types. The company responded that in routine practice ISM patients may progress to SSM or AdvSM due to biological progression or reclassification of disease resulting from availability of additional clinical, laboratory and BM information. Very low transition probabilities to these health states were applied by the company, in line with published natural history data and UK clinical expert opinion. The EAG additionally requested whether these small number of ISM patients progressing to SSM and AdvSM justify the additional modelling complexity (i.e. incorporating tunnel states). The company responded that although infrequent, progression to SSM or AdvSM is associated with substantially higher morbidity, HCRU and costs, as well as distinct management pathways and prognosis compared to ISM. It further argued that the inclusion of tunnel states had a small impact on the overall model results and improves the face validity and alignment with the known natural history of the disease. The EAG is satisfied with the company's responses and considers the inclusion and modelling of SSM and AdvSM to be appropriate.

4.2.3 Population

Consistent with the NICE scope and MHRA licence indication, the population considered in the CS was adult patients with moderate to severe ISM who are inadequately controlled on SDT. The population modelled in the company's base-case analysis was informed by the moderate and severe population without dose escalation from PIONEER. Key baseline characteristics in the economic model are listed in Table 4.2 below.

Table 4.2: Key baseline patient characteristics used in the economic model

	Overall ITT/safety population in PIONEER (N=246)	Company base-case
Age (years, mean)	51	40*
Male (%)	27.2	27.2
Weight (kg, mean)	81.29	81.29
Based on Table 41, CS * Informed by clinical expert input. CS = company submission; ITT = intention-to-treat; kg = kilograms		

EAG comment: The main concerns of the EAG relate to: a) the generalisability of the modelled patient population to UK clinical practice, and b) the mismatch between the patient population addressed in the CS and the population used to inform modelled patient characteristics.

- a) The EAG questions the generalisability of the company's modelled patient population to UK clinical practice. In the company's base-case, the ISM population was defined using the moderate to severe PIONEER subgroup without dose escalation. In response to clarification, the company argued that UK clinical experts considered the trial population to be broadly generalisable to UK clinical practice except for age, as ISM would typically present earlier in life than the mean PIONEER baseline age (51 years). However, the EAG's clinical expert noted that the ISM-SAF threshold (i.e. TSS ≥ 28) used in the economic model and PIONEER may not fully capture the heterogeneity of symptoms seen in UK practice. Specifically, patients with severe pruritus (which could lead to suicidality) and skin lesions, with minimal flushing and no other systemic symptoms would fall below the threshold. The EAG's clinical expert further stated that symptoms like these should have more weight, and that patients with severely impacted HRQoL should be taken into account irrespective of ISM-SAF. This supports the EAG's concern in Section 4.2.2 of this report regarding the appropriateness of using the ISM-SAF TSS to classify disease severity in the company's model structure.

Additionally, the modelled mean starting age of 40 years in the company's base-case is substantially lower than the mean age of the overall ITT/safety population in PIONEER (51 years). In line with this population in PIONEER, the EAG's clinical expert reported a mean age of 51 years in their local ISM cohort. It is unclear to the EAG what the mean age and other patient characteristics of the moderate to severe subgroups with and without dose-escalation were in PIONEER, and it preferred to align its EAG base-case mean starting age with the PIONEER overall ITT/safety population and EAG clinical expert estimates.

Finally, the company excluded PIONEER patients who received avapritinib dose escalation (above the licensed UK dose). Although the EAG acknowledges that higher doses are not authorised in the UK, one EAG clinical expert noted that symptoms related to higher doses are similar to those of ISM anyway and patients with very high symptom burden may therefore consider this an acceptable risk in UK clinical practice. The other EAG clinical expert noted that dose escalation would not be part of UK clinical practice. Given this uncertainty, the EAG therefore explored the effect of including patients with the option for dose escalation in a scenario analysis.

- b) The EAG noted a mismatch between the patient population addressed in the CS (i.e. patients with moderate to severe ISM) and the population used to inform the modelled patient characteristics (i.e. the overall ITT/safety population in PIONEER). The age, sex and weight baseline characteristics specifically for the subgroup of patients with moderate to severe ISM in PIONEER are unknown to the EAG, and should be provided and explored in a scenario analysis by the company.

4.2.4 Interventions and comparators

The intervention considered in the CS was avapritinib + SDT, consistent with the anticipated UK summary of product characteristics (SmPC) and PIONEER trial. Avapritinib was modelled as 25 mg oral capsules QD. The company stated that patients treated with avapritinib were assumed to receive SDT at a reduced intensity to reflect the expected reduction in symptomatic therapy needs with effective treatment. Stopping rules for patients on avapritinib followed the PIONEER protocol, i.e. patients not responding to treatment (<30% TSS improvement) after the initial 24-weeks discontinued avapritinib and remained on SDT alone, whereas treatment responders ($\geq 30\%$ TSS improvement) continued avapritinib at the same dose.

In line with the NICE scope, the comparator considered was SDT alone, implemented as a blended basket of symptomatic therapies (Table 4.3).

Table 4.3: SDT basket for responders and non-responders in the avapritinib + SDT arm and patients receiving SDT alone

Comparator	Responders in avapritinib + SDT arm (%)	Non-responders in avapritinib + SDT arm (%)	Patients in SDT arm (%)	Source
H1-blockers (average)	97.4%	100.0%	100.0%	PIONEER
H2-blocker (cimetidine)	68.9%	66.0%	66.0%	
PPI (omeprazole)	17.2%	28.2%	28.2%	
Leukotriene inhibitor (montelukast)	37.7%	35.2%	35.2%	
Corticosteroid (prednisolone)	11.9%	9.9%	9.9%	
Cromolyn sodium (nalcrom)	32.5%	35.2%	35.2%	
Monoclonal antibody (omalizumab)	10.6%	9.9%	9.9%	
Off-label TKIs				
Midostaurin	0%	0%	9.9%	NICE TA728 ¹³
Imatinib	0%	0%	3.3%	Expert opinion ⁶ Buonomo (2022) ¹⁴
Dasatinib	0%	0%	1.1%	Buonomo (2022) ¹⁴ Verstovsek (2008) ¹⁵
H1/H2 = antihistamines; NICE = National Institute for Health and Care Excellence; PPI = proton-pump inhibitors; SDT = symptom-directed therapy; TA = Technology Assessment; TKIs = tyrosine kinase inhibitors				

All patients on SDT alone were assumed to remain on full SDT treatment for the modelled duration, whereas SDT for responders to avapritinib was assumed to be reduced by 50% based on the proportion of patients reduced by background therapy in PIONEER. The off-label TKIs included in SDT were modelled for a treatment duration of two years.

EAG comment: The main concerns of the EAG relate to: a) the generalisability of the SDT basket to UK clinical practice, b) assumptions related to modelling of the SDT basket.

- a) The EAG is concerned that the modelled SDT basket is not reflective of UK clinical practice. Firstly, for patients receiving SDT only, off-label TKIs (i.e. midostaurin, imatinib and dasatinib) were included, despite these being prohibited in PIONEER and currently not reimbursed in the UK. In response to clarification, the company stated that based on clinical expert engagement it was considered plausible that a small but non-negligible level of off-label TKIs are used in ISM. The company further stated that *“Off-label TKIs (e.g., midostaurin, imatinib, and dasatinib) were included in the base case based on observed studies indicating that TKIs have been used in a small, highly selected subgroup of non-advanced SM patients, although these agents are not routinely reimbursed or routinely used for ISM in the UK”*. The company further noted that its base-case use of the 2-year duration of off-label TKIs was considered a conservative approach and that evidence on typical duration in an ISM SDT context is limited. In other relevant NICE appraisals, durations of 3 years (TA728, midostaurin) and 5 years (TA1012, avapritinib) were reported. The EAG’s clinical expert was unable to comment on the appropriateness of including off-label TKIs in the SDT basket and its treatment duration. Considering the lack of reimbursement in the UK and exclusion of off-label TKIs in PIONEER (the primary source to inform modelled treatment effectiveness), the EAG excluded off-label TKI’s from the SDT basket in its base-case. Secondly, the EAG’s clinical expert highlighted that omalizumab is not licenced and difficult to obtain permission to use in this condition in the UK. Additionally, the proportion of patients on corticosteroids and cromolyn sodium seems also overestimated, as the EAG’s clinical expert stated that *“we don’t have many patients on corticosteroids for ISM in dermatology, and have about 5% dermatology patients on cromoglycate (more effective for neurocognitive problems)”*. Next to that, phototherapy and skin directed treatments (topicals) were added to the SDT basket by the EAG’s clinical expert. To address uncertainty surrounding the types of treatments in the SDT basket and the proportions of patients receiving these, scenario analyses should be explored including a SDT basket that is reflective of the EAG’s clinical expert inputs. Finally, the company included a single H2-blocker in their initial base-case SDT basket to represent H2-blockers. In response to clarification, an average dose and cost of multiple H2 blockers was included in their updated base-case, which the EAG considers appropriate.
- b) The EAG questions several company assumptions related to the modelling of the SDT basket. First, it was assumed that concomitant SDT therapy for avapritinib treatment responders is reduced by 50%. In response to clarification, the company argued that this assumption is supported by evidence from the PIONEER trial, in which approximately 54% of patients receiving avapritinib experienced an improvement (including reductions in dose or frequency, PRN use, or discontinuation of therapy) in at least one SDT medication class. The company further stated that given the heterogeneity of SDT regimens and the absence of sufficient longitudinal data, a uniform 50% reduction in SDT use among responders was applied as a pragmatic summary. The EAG agrees that evidence from the PIONEER trial seems to support reduced concomitant SDT use for avapritinib treatment responders, and the EAG’s clinical expert agrees with the company’s modelling assumption. However, the EAG considers the simplified 50% reduction assumption insufficiently justified, but noted that this assumption is likely not a key model driver as the impact on the CE seems minor. Secondly, the company assumed that patients receiving each treatment within the SDT basket were assumed to remain fixed over time, and patients were not permitted to switch between individual SDT components. The EAG questions whether this simplistic assumption is reflective of UK clinical practice, and the EAG’s clinical expert confirmed that patients in clinical practice do switch treatment, with trial and error to find which treatments work best for each individual patient. The

EAG's clinical expert additionally noted that treatment doses may change considerably within each category. The company stated in its clarification responses that overall, the modelling approach for concomitant and subsequent SDT use was consistent with patterns observed in PIONEER while adopting a simplified structure for the economic modelling. The EAG acknowledges the added modelling complexity required to reflect treatment switching over time and considers the company's approach sufficient.

4.2.5 *Perspective, time horizon and discounting*

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 4 weeks with a lifetime time horizon, and a half-cycle correction is applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 *Treatment effectiveness and extrapolation*

4.2.6.1 *Efficacy*

Key clinical parameters in the model were informed by data from the PIONEER phase 2, 3-part randomised, double-blind, placebo-controlled study and supplemented with external sources where necessary. The PIONEER February 2025 data cut was used for the base-case. Baseline characteristics, that is mean age, proportion male and mean weight, were derived from PIONEER (CS, Table 41).

For avapritinib, the company stated that they modelled efficacy in terms of response status, where patients with 30% reduction in TSS as assessed after 24 weeks of initial treatment were considered to have a response, in line with the criteria recommended by the European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) consortium (50% were used in a scenario). Patients were categorised into severity states (mild, moderate, severe based on TSS status) consistent with the PIONEER trial.¹¹ Health state occupancy was included in the model directly from the PIONEER TSS summary report. For this, the company did not use the full ITT population, but excluded patients with dose escalation and patients in the mild TSS state. For avapritinib, observed distributions were applied over the planned full trial follow-up (up to 252 weeks) (CS, Table 42). Beyond this period, patients were assumed to remain in their current state until discontinuation, after which they transitioned to the SDT health state distribution.

For the SDT arm, health state occupancy data were available only up to 24 weeks, after which patients in the clinical trial crossed over to avapritinib. In the model, observed distributions from PIONEER were applied during the first 24 weeks and thereafter SDT patients were assumed to return to their baseline health state distribution beyond 24 weeks and over a 24-week waning period. Patient-level data were used directly in the model for the length of the trial duration, i.e. for approximately 252 weeks in the avapritinib arm and 24 weeks in the SDT arm. Patients with missing observations were excluded for that cycle.

A small proportion of patients transitions to SSM and AdvSM. The probability for this transition was averaged over probabilities derived from three publications (i.e. the ECNM registry-based study, Spanish Network on Mastocytosis (REMA) 2009 study, and REMA 2013 study)¹⁶⁻¹⁸ and assumed to apply to the severe ISM state, while half of this probability was applied to the moderate ISM state and a quarter to the mild ISM state. This results in avapritinib indirectly affecting the likelihood of transitioning to SSM and AdvSM.

All-cause mortality rates specific to age and sex were applied in each cycle using UK Office for National Statistics (ONS) life tables.¹⁹ The company assumed that there was no differential mortality based on health state severity in ISM, but did apply a hazard ratio (HR) to increase mortality for all patients with ISM based on published evidence: among two available sources, UK clinical experts chose Kibsgaard (2020)²⁰ as more representative of observed practice than Mukherjee (2023),²¹ resulting in a modelled HR of 2.06. For SSM and AdvSM, the HR was 5.50 based on Tefferi (2019).²²

4.2.6.2 Duration of treatment

Patients discontinue treatment due to initial or long-term non-response or AEs. The initial response criterion used by the company led to [REDACTED] of patients continuing avapritinib treatment (CS, Table 42). In addition to this, United States (US) real-world evidence (RWE) was used to inform long-term TTD (US Specialty Pharmacy & PAP ISM patients RWE dataset).²³ The RWE cohort included [REDACTED] SM patients with a starting dose of 25 mg as a proxy for identifying ISM patients. The company performed survival analysis on this dataset, excluded distributions that would yield implausible results (Gompertz and generalised gamma, based on expert opinion) and then averaged the remaining distributions to yield a mean duration of treatment (DoT) of [REDACTED] years. It was unclear how this was implemented in the model. In addition, [REDACTED]% of patients in the avapritinib arm were assumed to discontinue during the first treatment cycle due to AEs.

EAG comment: The main concerns of the EAG relate to: a) likely under-estimation of avapritinib treatment duration, b) direct use of health state distribution trial data in model, c) potential disease progression is not fully reflected in the model and SDT long-term effectiveness assumed to be equal to baseline, d) trial population excluding patients with dose escalation and with mild TSS, e) progression to SSM and AdvSM, f) mortality benefit, g) in- or exclusion of crossed over patients in long-term avapritinib effect estimation, h) avapritinib patients staying in last observed health state after end of trial period, and i) 3-months treatment effect waning.

- a) Likely under-estimation of avapritinib treatment duration: The EAG was concerned that the company's model may be double-counting treatment discontinuation. As it was not transparently described, it is worth highlighting that there are three discrete, one-off discontinuation events in the company's model: 1. At week 8, [REDACTED] of patients discontinue due to AEs. 2. At week 24, only [REDACTED] of patients continue their treatment because the remainder of patients had insufficient response (model file, with the 30% TSS response criterion). 3. At [REDACTED] years, all patients remaining on treatment discontinue as it was considered unlikely that patients would continue treatment indefinitely. The company provided more information on these three components in its response to clarification question B9.
 - i. First, regarding **the treatment discontinuation due to AEs** in the first 24 weeks, the company explained that a one-off discontinuation rate of [REDACTED] was applied in model cycle 3, i.e. at week 12. The company stated that this was: "*based on the proportion of patients discontinuing avapritinib due to AEs observed in PIONEER by that timepoint*" (clarification response B9.b). It was still unclear to the EAG why this probability was only applied once at this timepoint, and whether after this timepoint no patients discontinued due to AEs in the trial. These patients are then re-distributed according to the SDT health state distribution. Further justification is required on the one-off implementation of discontinuation due to AEs.
 - ii. The **24-week stopping rule may not be appropriate**, as it was not in line with the evidence from the trial or the SmPC. The company clarified (clarification response B5.b) that the modelled 24-week stopping rule was not based on the SmPC, but is rather in line with the expectation that regular reassessment of treatment effectiveness will be performed, and a

6-month timeframe was considered clinically reasonable and appropriate, as confirmed by the company's clinical experts.

The stopping rule requires the use of TSS as the response assessment measure. One EAG clinical expert indicated that this is not routinely used in clinical practice and that it would not be the ideal measure outside of the research setting, particularly because very severe skin or other symptoms without systemic symptoms should not exclude patients from treatment. However, the other EAG clinical expert did indicate that it was increasingly used in clinical practice. In addition, when this stopping rule is applied in the model, the applicable response threshold is currently uncertain. Clinical experts (n=3) considered the 30% TSS reduction sufficient as a clinically meaningful threshold for response to avapritinib aligning with ECNM-AIM recommendations (clarification response B5.c). A 50% TSS reduction is considered more conservative with one clinical expert describing this a 'gold standard' based on their clinical experience.'

The stopping rule was also not in line with the evidence. Figure 1 (K-M curves) of the company's clarification response suggests that approximately [REDACTED] of patients in PIONEER remained on treatment at around week 24, while in the company's model it is only approximately [REDACTED] (see also K-M curve in Figure 1 of the clarification response). This also results in the modelled health state distribution not being in line with the observed health state distribution at 24 weeks, while in the previous model cycles the modelled health state distribution tracked that of the trial closely (Table 30 of the clarification response). In the trial, at week 24 a significant change occurred whereby more patients were in the mild ISM state compared with the model. The company provided a scenario where the stopping rule is disabled in Table 26 of the clarification response. Even when using this scenario there continues to be a mis-match between trial and model health state distribution at 24 weeks. The EAG requests that the company investigate the cause of this mis-match.

The company claims that there is no double-counting of treatment discontinuation: *"because the 24-week stopping rule and long-term discontinuation represent distinct mechanisms applied to different patient groups and time periods"* (Clarification response B9.c), but the EAG remained unconvinced by the company's arguments. While the EAG acknowledges that distinct mechanisms may be at play at different time points, the EAG has not been convinced that observed treatment discontinuation in the used real-world data or the trial do not in fact include those who discontinued due to lack of response that are now already modelled to discontinue at 24 weeks based on the company's response criterion. The company did not provide a comparison between observed discontinuation in the trial, the RWE and modelled discontinuation despite the EAG's request in clarification question B9.e, but did provide proportions of patients on treatment up to 60-months as observed in PIONEER. This clearly shows that at 60 months, approximately [REDACTED] of patients have discontinued, while in the model this number is [REDACTED].

Since this 24-week stopping rule results in a mismatch between model and trial, it is not a formal requirement and clinical practice will likely vary and there are doubts about the appropriateness of TSS for this purpose, the EAG considers that it should be removed from the company's model base-case and instead be explored in a scenario. The company is asked to explain the discrepancy between model and trial health state distributions and fix the implementation of the 24-week stopping rule if necessary.

- iii. **Regarding long-term treatment discontinuation**, the use of the US RWE data to inform it is questionable: first, it included patients recorded as having SM, and health states (mild, moderate, severe) were not recorded, and SM subtype information was incomplete, resulting in questionable generalisability to the population of interest. The company

attempted to mitigate this by only including patients with a starting dose of 25 mg in their analysis, as this is the starting dose used in ISM. Second, based on visual inspection of K-M curves (e.g. Figure 3 of the company's clarification response), data appears to have been available for approximately 30 months, that is a shorter time than in PIONEER (where data is available for up to 60-months). Given that people continue treatment for a long time and not many events have occurred, the survival analysis showed vast differences between plausible curves. The company recognised the limitations with the data and thus did not use these in the model. Instead, they presented the data to clinical experts and asked them to provide the expected average duration of treatment among patients who initially responded to avapritinib. This resulted in the company's estimate of [REDACTED] years. While this was described as the expected average duration of treatment, it is implemented in the model as a one-off discontinuation event (i.e. a maximum treatment duration), after which no cost for avapritinib is incurred, and after which patients are re-distributed to their baseline health state distribution (over 3 cycles). The EAG considers it uncertain how long treatment is continued after the end of the observed trial data. The company is likely to underestimate treatment duration because it implemented the mean expected treatment duration as estimated by experts as a maximum treatment duration.

Overall, for all aforementioned reasons, time on treatment in the model is likely underestimated, which leads to both an under-estimation of costs and benefits. The company could have fitted survival curves to its trial, and this would likely reduce some uncertainty, at least for the time that trial data are available. In conclusion, the EAG considers the stopping rule to be inappropriate, and also highlights significant uncertainty about treatment discontinuation in the model.

- b) Direct use of health state distribution trial data in model: the EAG was concerned that the company directly used trial data in the model as opposed to estimating transition probabilities, which may result in overfitting to the data. The company explained (clarification response B6.a) that treatment benefit is achieved early (within 3 to 6 months) and is then largely maintained over time, which would result in very low transition hazards beyond the early phase, making the estimation of reliable transition probabilities challenging. The company considered that the estimation of transition probabilities under these conditions may lead to sensitivity to assumptions and functional form choices. The company also mitigated the risk of overfitting in later cycles by requiring a minimum of 10 patients for deriving health state distributions. The EAG thought that the minimum of 10 patients may be low to obtain a stable health state distribution over three health states. It also noted that using this minimum results in an increase in the proportion of avapritinib patients residing in the mild health state in cycle 46 of the model. The EAG was wondering how likely it would be that people would transition from moderate to mild at this stage, or whether this was rather caused by lack of follow-up data in the moderate and severe health states. Given this uncertainty, the EAG preferred to use a minimum of 20 patients to calculate health state distributions. With this measure taken, the EAG agrees that the risk of overfitting may be offset by the difficulty of estimating transition probabilities and potential for inducing further uncertainty.
- c) Potential disease progression of ISM is not fully reflected in the model, SDT long-term effectiveness assumed to be equal to baseline: the EAG was concerned that the model does not fully reflect potential disease progression over time. Instead, the company assumed that patients in the SDT arm would revert to baseline after the end of the trial period (24 weeks for the SDT arm). The EAG was concerned that this assumption may reflect discontinuation of SDT, but the company explained that it rather reflects clinical expectations that patients receiving SDT would not be

expected to experience a sustained change in underlying symptom severity compared with baseline, as SDT does not alter the course of disease but provides symptom control (clarification response B7.a). As such, the company assumed that patients remaining on SDT would have a stable symptom burden over time, broadly consistent with their baseline severity. The EAG notes that better control of symptoms may translate into an impact on HRQoL also in the long term, without altering the course of the disease, which is now not captured in the model except through their health state distribution. In addition, there was no evidence of a reversal to baseline at the end of the SDT follow-up in PIONEER (24 weeks), where the percentage of patients with response continued to increase up to 24 weeks (CS, Figure 15). The EAG clinical experts both stated that disease progression was very variable, and that many did not progress from their initial health state but that some did, and it was difficult to predict who that might be. Figure 9 of the CS shows that a proportion of patients with lower symptom burden ISM does appear to progress to a higher symptom burden ISM.²⁴ In the absence of evidence on health state distributions over time in the SDT arm, the EAG considers it more appropriate that patients remain in the last observed health state. The company is asked to explore any evidence on the natural history of the disease.

- d) Trial population excluding patients with dose escalation and with mild TSS: the EAG was concerned that using this limited population may induce bias, particularly if dose escalation was employed when a lack of effectiveness was observed. The company responded (clarification response B5.a) that dose escalation to 50 mg in PIONEER Part 3 was a protocol-defined option and was not implemented as a routine escalation for patients who failed to respond. It was permitted only for patients who had previously demonstrated benefit and tolerability on avapritinib and subsequently experienced worsening of symptoms after entering Part 3. The company compared the health state distributions over time when including patients who had dose escalation to the company's base-case (i.e. excluding patients who had dose escalation) and found that the distributions of patients across mild, moderate, and severe health states were highly comparable between the two populations. The EAG's concern was therefore addressed. However, one of the EAG's two clinical expert stated that dose escalation would likely be used in clinical practice, for patients with partial response who tolerated the drug well, while the other suggested that it would not be used in clinical practice. To address this uncertainty, the EAG performed a scenario using the broader population where dose escalation was permitted and the costs of the escalated dose included.
- e) Progression to SSM and AdvSM: even though the evidence was not stratified by ISM symptom categories, the company assumed that progression rates predominantly applied to severe ISM and to a lesser extent to the moderate ISM state. The company justified this approach stating that patients with severe ISM were the subgroup most likely to reflect the higher-risk end of the ISM spectrum captured in observational cohorts reporting progression, particularly given that greater disease severity is generally associated with increased biological activity and higher likelihood of progression. The company noted that Matito (2013 & 2009).^{17, 18} show a clear severity gradient across diagnostic categories, with progression risk higher in more severe categories, but this related serum baseline tryptase levels rather than TSS health states to risk of progression. The EAG notes that the current model implicitly results in a treatment effect on the progression to SSM and AdvSM, which may be debatable, particularly in patients who were labelled as progressed but really were initially mis-classified. This treatment effect on the progression to SSM and AdvSM also results in a mortality benefit for patients on avapritinib as SSM and AdvSM states have a higher mortality HR than ISM. Given the limitations with the evidence, and the resulting uncertainty around the company's approach, the EAG suggests exploring a scenario in which the probability of progression to SSM and AdvSM does not depend on ISM health states. The EAG however noticed multiple errors in the implementation of the SSM and AdvSM probabilities. First, probabilities of

progression observed in studies with longer observation periods were incorrectly converted to the model cycle length. Second, the model assumes that progression in the avapritinib arm only starts in Cycle 7, while in the SDT arm it starts in Cycle 0. To the knowledge of the EAG this was not justified, and therefore this might be an error. Multiple additional potential errors were found in the programming of transitions to SSM and AdvSM states in the TSS sheet of the model, including a likely bracket or coding error in TSS sheet column AT (where the term ‘probSSMtoASM’ should be multiplied with all prior terms, not just the previous row), a rogue “+” in the formula in the TSS sheet column AA (which may not have an impact), referencing to wrong cells on the Distributions sheet (e.g. TSS sheet columns AA, AF and AG should likely reference to Distribution sheet AB:AD for those who had discontinued avapritinib and were thus following the SDT distribution); and use of instantaneous transition probabilities to SSM rather than cumulative probability of residing in SSM when calculating people that enter or reside in AdvSM (e.g. columns AA, AG and AT in TSS sheet). Because all these potential errors are distributed across multiple sheets and affect multiple other calculations, the EAG did not fix all these errors and would ask the company to carefully check the implementation of SSM and advSM transitions and apply amendments where necessary. The EAG recommends the following test: when transition probabilities to SSM and advSM are set equal across ISM health states, incremental LYs for avapritinib versus SDT should be zero. In the meantime, progression to SSM and AdvSM are disabled in the EAG base-case.

- f) A mortality benefit for avapritinib remains. This appears to be caused by a potential error in the model that the EAG could not address in the short time. The EAG requests that the company provides a corrected model file that calculates the same progression probabilities to SSM and AdvSM independent of prior health states and independent of treatment arm. In addition, the EAG also corrected an error in the conversion of the observed probabilities to the model cycle length.
- g) It was unclear to the EAG whether patients who had crossed over to the avapritinib arm after week 24 were included in the avapritinib arm in the model. The company’s response was contradictory: *“The OLE data used to inform the avapritinib arm did not include patients who crossed over from SDT to avapritinib after the initial 24-week period. Following crossover, these patients were treated as avapritinib recipients and contributed to the avapritinib health state distributions from that point onwards”* (clarification response, B6.d). In addition, the company’s scenario excluding crossover patients provided in Table 27 of the clarification response shows no impact. According to the model file, it appears as though these patients are not included in the longer-term modelling, as patient numbers do not increase after that time point, however it could be that there was more attrition than cross-over. The company is asked to confirm that the patients who crossed over from SDT to avapritinib are not included in the avapritinib arm of the model and include a scenario analysis with these patients included.
- h) Assumption that after the trial period ends, patients in the avapritinib arm remain in their last observed health state until they discontinue treatment: the company provided further context for this assumption (clarification response B6.c), explaining that in the final 2 years of available OLE data, transitions between symptom severity health states were infrequent. Furthermore, the company provided an analysis of patients who did change health state during this later period, which showed that the average within-patient change in TSS was small, with changes clustered around health state thresholds rather than reflecting substantial shifts in symptom burden. The EAG agrees that the assumption is reasonable.
- i) When patients discontinue avapritinib, they experience a 3-months treatment effect waning period, after which they follow the SDT health state distributions. This assumption was informed by UK clinical expert input, who advised that loss of treatment effect following discontinuation would be expected to occur within a 3-to-6-month timeframe, depending on the reason for discontinuation and individual patient characteristics. The company acknowledged that patients who discontinue

due to loss of response may have experienced waning prior to formal treatment discontinuation, but others discontinue due to AEs and may experience a treatment benefit for longer. They therefore considered their choice conservative. The EAG notes uncertainty about the 3-months treatment effect waning assumption.

4.2.7 AEs

The incidences of AEs included in the model were based on Grade 3–4 events reported in the PIONEER trial. Each AE was assigned a one-off cost, based on NHS reference sources, and a disutility value, informed by published literature. The total AE-related costs and disutilities were calculated by multiplying the incidence of each AE by its associated unit cost and disutility. Anaphylaxis was modelled separately using data from the Perceptions Realities and Insights on Systemic Mastocytosis (PRISM) study, with higher incidence assumed under SDT and a reduced risk applied for avapritinib (CS, Table 49). **EAG comment:** The EAG was concerned whether a one-off modelling of 14-day cost and HRQoL impact for AEs was appropriate. In response to clarification question B10, the company extended AE duration to 28 days in a scenario, that had only a very small impact on CE estimates. The EAG considers the company's modelling of AEs appropriate.

4.2.8 HRQoL

Treatment-independent utility values were applied to each ISM severity state (mild, moderate, severe) as well as the SSM and AdvSM health states. In addition, a utility adjustment was added to avapritinib patients who achieve the TSS response threshold ($\geq 30\%$ reduction) but remain in the severe health state. The adjustment was an increase of their utility by 50% of the difference between the moderate and severe health state ().

4.2.8.1 To adjust utilities for ageing, age-specific utility values from the general UK population by Hernández-Alava (2022)²⁵, in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 12,²⁶ were used. HRQoL data identified in the literature review

According to the CS, the SLR identified 17 studies reporting HRQoL data. The company considered none of the studies from the SLR for the economic model, because they were all related to the PIONEER trial or there was a lack of relevance to the health states being used in the economic model.^{5, 27}

4.2.8.2 Health state utility values

The utility values for each of the ISM severity states were informed by EQ-5D-5L data, collected within the PIONEER trial Part I,²⁷ mapped to EQ-5D-3L using the Hernández-Alava (2022) crosswalk algorithm.²⁸ For SSM, the utility value was based on the Dutch Expert advisory board²⁹, and for AdvSM the utility was informed by NICE TA1012³⁰ and the PATHFINDER trial³¹; a multi-centre, open-label, single-arm study on 107 patients with all subtypes of AdvSM. A summary of all utility values used in the company's base-case CEA is provided in Table 44.

Table 4.4: Health state utility values

Health state	Utility value	Reference	Justification
Mild		PIONEER trial ^{11, 27, 32}	Utility of ISM health state by TSS changes in PIONEER trial was selected because disease symptom severity (mild,
Moderate			
Severe (non-responder)			

Health state	Utility value	Reference	Justification
Severe (responder)	██████████		moderate and severe) was the strongest predictor of patient utility.
SSM	██████████	Dutch Expert advisory board ²⁹	EQ-5D data was not collected for SSM and AdvSM, so EQ-5D data from the best available alternate source was used.
AdvSM	██████████	NICE TA1012, ³⁰ PATHFINDER trial ³¹	EQ-5D data was not collected for SSM and AdvSM, so EQ-5D data from the best available alternate source was used.
Based on Table 51, CS In response to clarification question B12, the company corrected the utility value for the severe health state from ██████████ AdvSM = advanced systemic mastocytosis; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ISM = indolent systemic mastocytosis; NICE = National Institute for Health and Care Excellence; SSM = smouldering systemic mastocytosis; TA = Technology Assessment; TSS = total symptom score			

4.2.8.3 Disutility values

AE disutilities were informed by published literature and UK clinical expert opinions.⁶ Each disutility value was corrected for the cycle probability, reported in CS, Table 49, and the duration of the corresponding AE, assumed to be 14 days according to CS, Table 53.

- a) **EAG comment:** The main concerns of the EAG relate to: a) the utility benefit for avapritinib responders, b) handling of EQ-5D data from PIONEER to inform the ISM health state utilities, c) source to inform the AdvSM health state utilities, and d) sources to inform the disutilities of anaphylaxis with(out) complications. The company applied a utility benefit to avapritinib responders ($\geq 30\%$ reduction in TSS) who experience clinically meaningful symptom improvement but remain in the severe health state. In response to question B11, the company clarified that the increase in utility: “reflects a modelling interpretation informed by Dutch and UK clinical expert input. “Across Dutch advisory board discussions and UK clinical expert inputs, clinicians consistently stated that a $>30\%$ reduction in TSS represents a clinically meaningful important in symptoms”. The EAG is concerned that applying this utility benefit would introduce double-counting because the utility values used in the model and based on PIONEER also included the observations from treatment responders experiencing clinically meaningful symptom improvement without transitioning to a less severe health state. The company disagreed and said that: “the response adjustment corrects for a structural limitation of using average health state utilities and ensures that within-health state improvements associated with treatment response are captured for avapritinib, rather than duplicating benefits already included in the PIONEER-derived utility estimates.” However, the EAG remains concerned because the company presented no evidence that utility values do not capture symptom improvements appropriately, and if a 30% TSS reduction represents “clinically meaningful improvement” sufficient to warrant a utility increment of 50%, it raises the question of whether the health state thresholds are appropriately defined. The EAG thus excluded the utility benefit to avapritinib responders in the base-case.
- b) Information regarding HRQoL data, including the pattern of missingness and how missing data were handled, was lacking in the CS. In response to clarification question B12, the company confirmed that no imputation was applied in the base-case and analyses used observed data only.

Cross-sectional ordinary least squares (LS) regression estimated health state-specific utilities (EQ-5D regressed on TSS severity categories, no additional covariates). As a sensitivity analysis, Last Observation Carried Forward (LOCF) was used. However, the EAG has several concerns. It remains unclear which patient population was used for the EQ-5D analysis. Table 33 (from their clarification response) appears to include patients in the mild health state, which is inconsistent with the modeled population (moderate and severe, without dose escalation from PIONEER). Table 33 (from clarification response B12) also shows missing data increased from 0.5% at baseline to 94% at week 76, followed by persistently high rates from week 52 onwards. Critically, Table 33 reports only overall missing data rates at each timepoint, without breakdown by TSS severity category or treatment allocation (avapritinib versus placebo). This lack of transparency prevents assessment of whether dropout patterns differ systematically. However, the substantial increase and time-varying pattern of missingness indicates data are not missing completely at random (MCAR), yet the company's observed-data-only approach implicitly assumes MCAR. Guidance states that complete case analysis should not be used in the base-case, and that single imputation methods like LOCF have been shown to bias parameter estimates even if data are MCAR.³³ Additionally, omitting covariates, such as baseline characteristics, likely introduces omitted variable bias. The company stated it did not pursue Mixed Models for Repeated Measures (MMRM) because: *“this would require additional assumptions.”* However, their current chosen approach also requires strong assumptions. Therefore, the EAG considers the company's current approach inadequate and recommends implementing MMRM or Multiple Imputation (MI) in the base-case.

- c) The company stated that the AdvSM utility value was aligned with NICE TA1012, utilising estimates from the PATHFINDER trial. During expert consultation, both Dutch and UK clinical experts were asked to review the health state utility values. While objections were raised regarding the SSM utility value (which the company subsequently adjusted in the base-case), only one expert noted that AdvSM is a heterogeneous group and the utility value may depend on the subgroup. No specific concerns about the magnitude of the AdvSM utility value were raised by experts. However, the EAG identified an unexplained discrepancy between the AdvSM utility value presented to experts (██████) and that used in the economic model (██████). In the company's response to clarification question B12f, the company continues to cite the PATHFINDER trial EQ-5D data as the source, and the EAG cannot see either utility value in that source. The justification for this difference remains unclear for the EAG, but changing the utility value from ██████ to ██████ has minimal impact on CE.
- d) The company applied a disutility of 0.09 for anaphylaxis without complications, sourced from Shaker (2019) and NICE TA769. For anaphylaxis with complications, the company assumed a disutility of 0.18, double that of uncomplicated anaphylaxis. They stated in their clarification response B13e that: *“neither Shaker et al. (2019) nor TA769 provides a separate EQ-5D disutility specifically labelled 'anaphylaxis with complications' versus 'without complications'.”* Furthermore, Figure 11 in the clarification letter B13b shows that in TA769 the same disutility (0.09) for both mild and moderate anaphylactic reaction is used. This suggests that the available evidence does not support a doubling of impact for anaphylaxis with complications, but given the minimal impact on the CE and no evidence for a better alternative, the EAG is satisfied with the company's approach.

4.2.9 Resources and costs

The cost categories included in the economic model were treatment costs (drug acquisition costs and administration costs), health state unit costs and resource use (including costs associated with SSM and AdvSM), and costs of managing AEs.

4.2.9.1 Unit prices were based on the NHS reference prices, British National Formulary (BNF)³⁴, and Personal Social Services Research Unit (PSSRU).³⁵ Where necessary, costs were inflated to 2024/25 prices using the hospital and community health services (HCHS) pay and prices index from the Unit Costs of Health and Social Care.³⁶ ■Resource use and costs data identified in the literature review

4.2.9.2 According to the CS, the SLR identified eight studies reporting resource use and cost information. The company considered none of the studies to be useful for the economic model, because they had limited applicability to UK clinical practice. ■Treatment costs (with Patient Access Scheme [PAS])

All primary treatments in the company's economic model were costed per mg. The assumed dosing schedule for all treatments were informed by the respective SmPCs and UK clinical expert opinions⁶, presented in CS Table 56. For avapritinib, the recommended dose is 25 mg orally QD. Drug wastage was not discussed in the CS.

Acquisition costs for avapritinib were sourced from BNF (2025), and a simple patient access scheme (PAS) discount of ■■■■■ was used, in line with the AdvSM appraisal.³⁰

Acquisition costs for the basket of SDT were taken from the electronic market information tool (eMIT, 2024/2025) where possible, otherwise from the BNF (2025). For H1-blockers, an average cost was calculated in Table 55 of the CS. Table 54 gives a summary of drug acquisition cost per cycle for avapritinib and the basket of SDT.^{37, 38}

For avapritinib treatment responders, the company assumed SDT background therapy to be reduced by 50%.

Administration costs were only applied to omalizumab, as the rest of the treatments are oral therapies. Omalizumab is administered through subcutaneous (SC) injection, and therefore associated with a cost of a 30-minute appointment with a Band 6 nurse, sourced from the latest PSSRU.³⁵

4.2.9.3 Health state costs

Disease monitoring and management costs were based on a Dutch advisory board.²⁹ The level of resource usage is largely determined by the level of disease severity in ISM, along with a predicted further reduction for patients who respond to avapritinib (CS, Tables 58 and 59). The reduction in resource use for responders is assumed to be applied 1 year following the start of treatment. SSM and AdvSM patients are assumed to have the same frequency and nature of resource use as the severe (non-responder) health state in Table 4.5.

Additionally, a one-off cost is applied to an assumed 10% of SSM or AdvSM patients who may be eligible for haematopoietic stem cell transplantation (all-HSCT). The cost for all-HSCT was estimated from the NHS National Cost Collection database,³⁶ combining codes SA38A, SA38B, SA39A, SA39B and SA40Z. Other subsequent treatments were not discussed in the CS.

Table 4.5: Health state costs by TSS

Health state	Resource use cost per cycle	Reference	Justification
Mild (non-responder)	£1,510.32	NICE TA708 ³⁹	Dutch advisory board ²⁹
Mild (responder)	£1,288.48	NICE TA534 ⁴⁰	

Health state	Resource use cost per cycle	Reference	Justification
Moderate (non-responder)	£1,800.52	NICE TA753 ⁴¹ PRISM study ⁴²	
Moderate (responder)	£1,536.24	NICE TA883 ⁴³	
Severe (non-responder)	£1,888.99	NICE TA778 ⁴⁴	
Severe (responder)	£1,611.71	NICE TA838 ⁴⁵ NICE TA814 ⁴⁶	
Based on Table 62 and 63, CS In response to clarification question B18, the company corrected the cost for disease health states by TSS based on the model sheet “RU and indirect costs” CS = company submission; NICE = National Institute for Health and Care Excellence; TA = Technology Assessment; TSS = total symptom score			

4.2.9.4 Event costs

Unit costs for the management of Grade 3-4 AEs were included as a one-off costs in the first cycle of the economic model, and calculated by multiplying the incidence of each AE (CS, Table 49), by its associated unit costs (CS, Table 65). The unit costs were taken from the eMIT and PSSRU 2024/25.^{35,38} Resources used to manage each AE were identified from published sources, including NICE TA728 and BNF.^{13, 34}

EAG comment: The main concerns of the EAG relate to a) sources for health state unit costs and resource use, b) acquisition cost calculation, and c) excluding subsequent treatment for AdvSM patients.

- a) The company stated in the CS that a Dutch advisory board was consulted for the frequency and nature of health state unit costs, but the EAG could not find this information in the cited reference. However, they could find information from UK clinical experts and questioned why these inputs were not used to support assumptions regarding resource use. In response to clarification question B16d, the company said that a secondary Dutch advisory board was used, and they corrected the reference. Two Dutch clinical experts were asked to adjust the frequency estimates from the global model, reflecting the English setting in terms of HCRU, to what they expected to best reflect Dutch clinical practice, making the distinction between HCRU associated with all patients and those patients featuring a stable response. The company preferred using their information instead of using information from UK clinical experts and justified this by stating that they used: “*the more conservative option.*” The EAG notes that for the resource use of neurologic domain: outpatient visits and full blood count for avapritinib responders, following the Dutch expert opinions does not result in the most conservative option. The UK clinical experts also commented that there might be an increase in blood monitoring, translating into an additional monitoring cost associated with avapritinib. Furthermore, the Dutch clinical experts were asked to make a distinction between HCRU for responders and non-responders, not differentiating per health state. It is thus unclear whether Dutch clinical experts were aware that a responder benefit was added on top of the benefit of residing in milder health states. It is also unclear how the company used this information from the Dutch clinical expert because health state unit costs differed not only per response but also per TSS health state in the model. In addition, it appears that the company applied this responder benefit to all patients on avapritinib treatment after 1 year of treatment. This works when the company’s modelled response assessment is active, by which patients who do not respond discontinue treatment with avapritinib. However, when this is disabled, as is done in the EAG base-case, this responder benefit on resource use is applied to all patients who remain on avapritinib treatment. The EAG explored removing the responder benefit on HCRU in the scenario analysis.

- b) In response to clarification question B15, the company clarified that: *“the current model implementation reflects pack-based dispensing for avapritinib and oral SDTs. For avapritinib, pack presentations are aligned to monthly supply. The model therefore assumes one pack per monthly cycle while patients remain on treatment, and applies the full pack cost in the cycle in which discontinuation occurs (i.e. no prorating within cycle).”* However, while the model assumes a 28-day cycle length, an avapritinib pack contains 30 tablets. This misalignment was adjusted by the company, but could potentially cause problems at discontinuation, where, depending on the time that patients discontinue they may have a varying amount of avapritinib in the pack, potentially leading to wastage that is now not accounted for. Furthermore, the acquisition cost formula for avapritinib during dose escalation appears to contain errors: the PAS discount is not applied, and a "flat pricing" option has been activated without supporting information or justification in the CS or clarification letter. The EAG considers that wastage scenarios should be explored by the company and it fixes the above problems with the dose escalation costs in the scenario analysis where the population potentially having dose escalation is included.
- c) The EAG found that avapritinib is also indicated as monotherapy for patients with AdvSM from the SmPC, but the costs related to subsequent avapritinib seemed to not have been included for patients who progress to AdvSM. In response to clarification question B17b, the company provided a scenario analysis including avapritinib as a subsequent treatment for AdvSM. Furthermore, midostaurin was also identified as an alternative first-line treatment option to avapritinib for AdvSM but there is uncertainty regarding how midostaurin and avapritinib will be positioned relative to each other. Therefore, the company explored another scenario in which patients receive a 50/50 split between avapritinib and midostaurin as first-line AdvSM treatment. The EAG prefers to include only avapritinib, with median DoT of 42 months based on TA1012, as subsequent treatment for AdvSM in the scenario analysis because midostaurin is currently not licenced or reimbursed for this population. However, because transitions to SSM and AdvSM are disabled in the EAG base-case, due to the multiple errors, this scenario analysis has not been performed.

4.2.10 Disease severity

A QALY shortfall analysis was performed in line with NICE manual and NICE DSU TSD 23.⁴⁷ The expected general population mortality values were taken from the ONS Life Tables for the years 2017-2019. The expected general population utility values were derived from the EQ-5D-3L value set from the MHV study. Total discounted QALYs for treatment-naïve ISM patients treated with SDT were derived from the company's economic model. The sex distribution (female 73%), starting age (40) and discount rate (3.5%) were in line with the base-case economic model prior clarification. The expected discounted QALYs for people without ISM were 18.68, and the expected undiscounted life years were 35.17. Patients with SDT were modelled to accrue 10.33 discounted QALYs, resulting in an absolute shortfall of 8.35 and a proportional shortfall of 44.69% (see Table 4.7). Hence, a severity modifier of x1.0 was applied (see Table 4.6).

Table 4.6: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality adjusted life year		

Table 4.7: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with ISM on current SoC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
18.68	10.33	8.35	44.69%	1.0
Based on Table 66 in CS CS = company submission; ISM = indolent systemic mastocytosis; QALY = quality-adjusted life year; SoC = standard of care				

EAG comment: The main concerns of the EAG relate to the updated company base-case in response to the clarification letter.

In response to clarification question B20, the company provided new QALY shortfall results because the previously reported values in the CS were affected by both a calculation error and the use of a non-preferred calculator setting. The updated QALY shortfall results presented by the company were validated by the EAG using the calculator by Schneider et al. Using a starting age of 40 years (company's base-case), proportion female 73%, a 3.5% discount rate, and 10.51 expected discounted QALYs for patients on SDT (in line with the updated economic model), the EAG found absolute and proportional QALY shortfalls of 7.33 and 0.4108 respectively. Although these results deviate from the results reported in the clarification letter by the company (7.51 and 0.4209) because patients with SDT were still assumed to accrue 10.33 discounted QALYs (in line with economic model prior clarification), this does not affect the modelled severity weight of 1.0x. Using a starting age of 51 years (EAG base-case), proportion female 73%, a 3.5% discount rate, and 10.51 expected discounted QALYs for patients on SDT (in line with the updated economic model), the EAG found absolute and proportional QALY shortfalls of 4.56 and 0.3027 respectively. This does not affect the modelled severity weight of 1.0x.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

All reported results are based on the original CS, prior to the EAG clarification phase.

The CS base-case CE results (probabilistic) indicated that avapritinib is both more effective (incremental QALYs of [REDACTED]) and less costly (reduced costs of [REDACTED], including PAS for avapritinib), and therefore a dominant strategy when compared to SDT (see Table 5.1). The deterministic incremental net health benefit (NHB), at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, were [REDACTED] and [REDACTED], respectively. The deterministic incremental net monetary benefit (NMB), at WTP thresholds of £20,000 and £30,000 per QALY gained, were [REDACTED] and [REDACTED], respectively.

Table 5.1: Summary of the initial company pairwise probabilistic results

Treatment	Total costs (£)	Total QALYs	Incr. cost (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Avapritinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SDT	[REDACTED]	[REDACTED]					

Based on Table 77 in CS, deterministic NHBs are based on Table 75 of the CS
 CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; QALY = quality-adjusted life year; SDT = symptom-directed treatment

Overall, the technology is modelled to affect QALYs by:

- Increased duration in the mild disease state ([REDACTED] QALYs, [REDACTED] the total incremental QALYs)
- Reduced duration in the severe disease state ([REDACTED] QALYs, [REDACTED] of the total incremental QALYs)

Overall, the technology is modelled to affect costs by:

- Increased drug acquisitions costs of avapritinib ([REDACTED], [REDACTED] the total decreased costs)
- Decreased drug acquisitions costs of SDT ([REDACTED] [REDACTED] the total decreased costs)

EAG comment: The company updated its base-case in response to the clarification letter, including the new blended basket of H2-blockers, the corrected UK tariff utility values for severe health state, and the corrected starting SDT health state distribution in the economic model. In the company's updated base-case, avapritinib is associated with incremental QALYs of [REDACTED] and a cost saving of [REDACTED], versus SDT. The incremental NHB, at WTP thresholds of £20,000 and £30,000 per QALY gained, were [REDACTED] and [REDACTED] respectively. Results of the updated probabilistic company base-case are reported in Table 5.2 below.

Table 5.2: Summary of the updated company pairwise probabilistic results

Treatment	Total costs (£)	Total QALYs	Incr. cost (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Avapritinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SDT	[REDACTED]	[REDACTED]					

Based on Table 77 in CS
 CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; QALY = quality-adjusted life year; SDT = symptom-directed treatment

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA) with 1,000 Monte Carlo simulations, deterministic sensitivity analyses (DSA) with selected parameters varied $\pm 20\%$ around the base-case value when no 95% CI information was available, as well as scenario analyses. The probabilistic incremental cost-effectiveness ratio (ICER) was consistent with the deterministic analysis. The probabilistic CS base-case analyses, including PAS, indicated CE probabilities of [REDACTED] and [REDACTED] at WTP thresholds of £20,000 and £30,000 per QALY gained. Moreover, the 95% percentiles for the probabilistic decreased total costs and increased total QALYs were ([REDACTED] - [REDACTED]) and ([REDACTED] - [REDACTED]), respectively (CS, Table 77).

The parameters that have the greatest impact on the ICER (based on the company's one-way sensitivity analyses prior clarification, with PAS discount) were:

- Anaphylaxis with complications
- Average time on treatment
- Midostaurin: cost per package

Avapritinib remained cost-effective or dominant in almost all scenarios. The following CS scenarios had the largest impact on the ICER:

- TKI usage 0% (increased the ICER by [REDACTED])
- 50% resource use reduction (decreased the ICER by [REDACTED])
- Time on treatment 5 years (decreased the ICER by [REDACTED])
- Midostaurin usage -5% (increased the ICER by [REDACTED])
- 0% resource use reduction (increased the ICER by [REDACTED])
- 25% resource use reduction (decreased the ICER by [REDACTED])
- After clarification: excluding stopping rule (increased the new ICER by [REDACTED] scenario analysis provided in response to the clarification letter).
- After clarification: TKI subsequent treatment (increased the new ICER by [REDACTED] scenario analysis provided in response to the clarification letter).

EAG comment: The main concerns of the EAG relate to: a) issues related to the probabilistic sensitivity analysis, b) issues related to the deterministic sensitivity analysis, and c) issues related to the scenario analysis.

- The EAG identified multiple issues related to the company's PSA. In response to clarification question B22, the company did a full review of the PSA parameterisation. However, the EAG noted that there were still relevant parameters omitted from the PSA e.g., "Years of TKI treatment", "Advanced disease costs", "Mortality rate ratios per health state". Furthermore, the EAG could not reproduce the exact probabilistic results due to the use of a random seed.
- The EAG identified multiple issues related to the company's DSA. In response to clarification question B21, the company clarified that: *"All parameters that are potentially suitable for deterministic sensitivity analysis were included in the DSA parameter list as part of a comprehensive and standardized DSA setup, regardless of whether the corresponding functionality was active in the base-case model at the time of submission."* They also said that the DSA trace formulae were revised in the new model version to ensure that all parameters are captured, but this seemed not to be the case. For completeness and transparency, the EAG believes a complete DSA is required even though the last (additional) parameters, primarily related to AEs, might not *"materially influence the ICER"*.

- c) In response to the clarification letter, several scenarios were added in the model. The EAG was not able to replicate scenario “Health state occupancy excluding crossover patient”, and that resulted in the exact base-case results of the company’s updated model (Table 46 in the clarification letter). The EAG was also unable to replicate scenario “Avapritinib and midostaurin as treatment for AdvSM” because the cost calculation was incorrect.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

Model structure, key assumptions, and input parameters were reviewed and validated by three UK clinical experts and incorporated with Dutch consultant opinions with expertise in the management of SM.

5.3.2 Technical verification

Quality-control procedures were undertaken, including verification of all input data with original sources, internal programme validation (checks of the model calculations, logical consistency, and data references), review of model interface and Visual Basic for Application code to confirm correct operation and data flow, and cross-checking of model outputs against expected clinical and economic patterns.

5.3.3 Comparisons with other technology appraisals

In response to the clarification letter, the company stated that there are no directly comparable published NICE TAs with a sufficiently similar DP to support meaningful cross-validation of the company’s economic model for avapritinib in ISM.

5.3.4 Comparison with external data

In response to the clarification letter, the company stated that external validation focused on clinical plausibility and alignment with UK practice. Model structure and key assumptions were validated through UK clinical expert input. Clinical effectiveness, health state occupancy and utility input parameters were derived from trials (particularly PIONEER), and supported by assumptions based on clinical expert input. Resource use and costs were informed by expert input and standard NHS costing sources.

Face validity was assessed through a combination of evidence-based review and structured clinical expert input.

EAG comment: The main concerns of the EAG relate to: a) technical verification of the economic model and b) lack of cross-validation with other relevant NICE TAs.

- a) The company stated in the CS that: “*Comprehensive quality-control procedures were undertaken to ensure the accuracy and integrity of both the model simulation and its conceptual implementation*”. However, despite the company’s effort, the EAG identified various errors within the economic model related to the implementation of the SSM and AdvSM transition probabilities (Section 4.2.6, EAG comment c). Next to that, the EAG requested completing the TECHNical VERification (TECH-VER) checklist and providing the results in its clarification letter. Although the company responded that the completed TECH-VER checklist were supplemented in their clarification responses, the EAG was unable to find it. The company should correct all errors in

the economic model and justify why these were not identified during their initial technical verification. A reassessment of technical verification should be provided as well as the completed TECH-VER checklist.

- b) In its clarification letter, the EAG requested cross-validation of the company's economic model structure, assumptions, inputs parameters and (disaggregated) outcomes with other relevant NICE TAs. The company responded that there are no directly comparable NICE TAs with a sufficiently similar DP to support meaningful cross-validation, mentioning TA1012 (avapritinib in AdvSM) than the most closely related one. In absence of relevant NICE TAs, the company instead focused on clinical plausibility and alignment with UK clinical practice based on trial data and UK clinical expert input. The EAG considers the company's justification of the lack of directly comparable NICE TAs for cross-validation to be sufficient.

6. EAGs additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the Key Issues related to the CE categorised according to the sources of uncertainty as defined by Grimm (2020)⁴⁸:

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the Key Issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the Key Issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler [2016]):⁴⁹

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Fixed error: removal of progression to SSM and AdvSM due to multiple errors (fixed error in conversion of probabilities to model cycle length, but not others) (Section 4.2.6)

6.1.1.2 Fixing violations

2. Disabled stopping rule after 24-week response assessment (Section 4.2.6)
3. Removed utility benefit for responders (Section 4.2.8)

6.1.1.3 Matters of judgement

4. Aligned mean starting age with the PIONEER overall ITT/safety population and EAG clinical expert estimate (Section 4.2.3): 51 years instead of 40 years
5. Excluded off-label TKIs from SDT basket (Section 4.2.4)
6. Used a minimum of data available for 20 patients instead of for 10 patients to calculate health state distribution (Section 4.2.6)
7. After trial end, SDT patients remain in their last observed health state instead of their baseline health state (Section 4.2.6)

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

8. Used wider population including dose escalation population and costs of escalated dose with correction to the calculation (Section 4.2.3 and 4.2.9)
9. Removed responder benefit on resource use (Section 4.2.9)

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of Key Issues related to the CE (conditional on FEs highlighted in Section 5.1)

Key Issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Appropriateness of using the ISM-SAF TSS to classify disease severity	4.2.2	Methods	Alternative disease severity classification	Unclear	No	Yes
Questionable generalisability of the company's modelled patient population to UK clinical practice	4.2.3	Bias & indirectness	Scenarios with alternative inputs	Unclear	Partly	Yes
Questionable generalisability of the SDT basket to UK clinical practice	4.2.4	Bias & indirectness	Scenarios with alternative inputs	Alternative scenario increases ICER	Partly	Yes
Likely under-estimation of avapritinib treatment duration and potential inappropriateness of 24-week stopping rule	4.2.6	Methods	Alternative estimation method	Unclear, the EAG's change substantially increases the ICER	Partly	Yes
Potential disease progression is not fully reflected in the model, SDT long-term effectiveness assumed to be equal to baseline	4.2.6	Bias & indirectness	Alternative estimation method	EAG's changes slightly increase the ICER	Yes	No
Progression to SSM and AdvSM is unequal in both arms, inducing a mortality benefit for patients on avapritinib	4.2.6	Methods	Correction of errors	Unclear: EAG's change decreases ICER but there are errors in the company's model	No	Yes
Utility benefit for avapritinib responders	4.2.8	Methods	Remove utility benefit	Slight increase in the ICER	Yes	Yes
Approach for the estimation of the ISM health state utilities	4.2.8	Methods	MMRM or MI	Unclear	No	Yes

Key Issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Resource use benefit for avapritinib responders	4.2.9	Transparency, Methods	Remove resource use benefit	Unclear. EAG analyses increases ICER	Partly	Yes
AdvSM = advanced systemic mastocytosis; CE = cost effectiveness; EAG = Evidence Assessment Group; FE = fixing errors; ICER = incremental cost-effectiveness ratio; ISM = indolent systemic mastocytosis; MI = multiple imputation; MMRM = Mixed Models for Repeated Measures; SAF = Symptom Assessment Form; SDT = symptom-directed therapy; SSM = smouldering systemic mastocytosis; TSS = total symptom score; UK = United Kingdom Notes: ^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator ^b Explored						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic and probabilistic* EAG base-case

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
Deterministic CS base-case									
Avapritinib	██████	██████	██████	-	-	-	-	-	-
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_1: Excluding SSM and AdvSM									
Avapritinib	██████	██████	██████	-	-	-	-	-	-
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_2: Disable stopping rule after 24-week response assessment									
Avapritinib	██████	██████	██████	-	-	-	-	-	-
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_3: Remove utility benefit for responders									
Avapritinib	██████	██████	██████	-	-	-	-	-	-
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_4: Align mean starting age with the PIONEER overall ITT/safety population and EAG clinical expert estimate									
Avapritinib	██████	██████	██████	-	-	-	-	-	-
SDT	██████	██████	██████	██████	██████	██████	██████	██████	██████
EAG_5: Exclude off-label TKIs from SDT basket									
Avapritinib	██████	██████	██████	-	-	-	-	-	-

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
SDT									
EAG_6: Use a minimum of data available for 20 patients instead of for 10 patients to calculate health state distribution									
Avapritinib				-	-	-	-	-	-
SDT									
EAG_7: After trial end, SDT patients remain in their last observed health state									
Avapritinib				-	-	-	-	-	-
SDT									
EAG base-case									
Avapritinib				-	-	-	-	-	-
SDT									
EAG_8 Scenario: Include dose escalation population and costs of escalated cost with correction to the calculation									
Avapritinib				-	-	-	-	-	-
SDT									
EAG_9 Scenario: Remove responder benefit on resource use									
Avapritinib				-	-	-	-	-	-
SDT									
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; LYs = life-years; NHB = net health benefit; QALY = quality-adjusted life-year; SDT = symptom-directed therapy; SSM = smoldering systemic mastocytosis; TKI = tyrosine kinase inhibitor; WTP = willingness-to-pay									

Table 6.3: Probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (WTP=25,000)	NHB (WTP=35,000)
Probabilistic CS base-case							
Avapritinib	██████	████	-	-	-	-	-
SDT	██████	████	██████	████	██████	████	████
Probabilistic EAG base-case							
Avapritinib	██████	████	-	-	-	-	-
SDT	██████	████	██████	████	██████	████	████
EAG_8 Scenario: Include dose escalation population and costs of escalated cost with correction to the calculation							
Avapritinib	██████	████	-	-	-	-	-
SDT	██████	████	██████	████	██████	████	████
EAG_9 Scenario: Remove responder benefit on resource use							
Avapritinib	██████	████	-	-	-	-	-
SDT	██████	████	██████	████	██████	████	████
AE = adverse event; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; LYs = life-years; NHB = net health benefit; SoC = standard of care; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness-to-pay Severity modifier of 1.0 is used for all analyses.							

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was [REDACTED] per QALY gained. The probabilistic EAG base-case analyses indicated CE probabilities of [REDACTED] and [REDACTED] at WTP thresholds of £25,000 and £35,000 per QALY gained. The most influential adjustments were excluding off-label TKIs from the SDT basket and disabling the stopping rule after a 24-week response assessment. The ICER increased most in the scenario analysis with alternative assumptions regarding dose escalation of avapritinib.

6.4 Conclusions of the cost effectiveness Section

The company presented a health economic model in line with the NICE reference case. Notable uncertainties in how the CS addressed the DP are related to the questionable generalisability of the company's modelled patient population to UK clinical practice, and in the comparators, as the company included off-label TKIs. The impact of the former is unknown, while the exclusion of the off-label TKIs increased the ICER as the inclusion of off-label TKIs in the SDT arm was a substantial driver of the SDT arm costs. The EAG was also concerned that there may be a potential mismatch between the disease severity classification in the company's model structure and UK clinical practice, which may have resulted in patients being classified as having mild disease (i.e. not eligible for avapritinib) in the company's model, while these would potentially be treated with avapritinib in UK clinical practice.

Important uncertainties were observed in the company's modelling of treatment effectiveness: first, the company's approach of modelling three discrete treatment discontinuation events (due to AEs, stopping rule and long-term all-cause) likely led to significant under-estimation of the avapritinib treatment duration. The modelled treatment response assessment and stopping rule in particular was considered by the EAG as likely inappropriate given that it was not in line with the evidence or the SmPC. It also led to significant under-estimation of the modelled number of patients on treatment over time compared with the evidence from PIONEER and RWE, and hence total avapritinib treatment costs. The EAG would like to see survival analyses performed on PIONEER TTD events. Second, the company made assumptions regarding treatment benefits for responders versus non-responders in addition to improvements in health states. In the company submission, responders experience, a within-health state utility benefit, which was not evidence-based and may induce double-counting as utilities were derived from a mix of responders and non-responders in the PIONEER study. Similarly, the company assumed a within-health state responder benefit in terms of a reduction in resource use, which was based on expert opinion and not transparently reported. Instead of only having been applied to responders, it appeared to have been applied to all patients treated with avapritinib when the company's response assessment is disabled. The EAG considers that further justification for this approach and further evidence to support this are required. These two responder benefits raise further questions about the appropriateness of the health states in the company's model as these, according to the company, do not fully capture the effect of avapritinib.

Second, the company's model ignored the potential natural history of the disease as no transition probabilities were estimated beyond the end of the trial period; the company assumed that patients either stayed in the last observed health state (avapritinib arm, until they discontinued) or went back to baseline after the end of the trial period (SDT arm). As there is uncertainty about the natural history of ISM, and indeed, many patients may never progress, assuming that patients broadly stay in their initial health states may be appropriate, but the EAG considered that assumptions about whether they go back to baseline or remain in their last observed health states should be consistent across arms. In addition,

small patient numbers at the end of follow-up may result in unstable health state distributions. Third, there were errors in the company's implementation of progression to smouldering and advanced SM and the EAG considered it questionable whether avapritinib could lead to a benefit in longevity through the reduction of progression to SSM and AdvSM in milder ISM states, as was modelled by the company without providing sufficient evidence as justification.

Lastly, the EAG requested further analyses on the estimation of ISM health state utilities as missing data were not appropriately handled and the EAGs requested approach (analysing longitudinal data using MMRM) was not used.

In conclusion, there is uncertainty about the CE of avapritinib versus SDT in this population. A lot of this uncertainty pertains to methodological uncertainty, which should be addressed through alternative modelling choices or further substantiation, including on: whether avapritinib indeed slows progression to SSM and AdvSM and therefore leads to an indirect benefit on life-years; survival analysis on PIONEER TTD data; and re-estimating utility values from PIONEER while addressing missingness. At the core, this is a rare disease with limited information about its natural history, resource use, and appropriateness of health state classification, and some uncertainty will likely remain. Further data collection will likely not lead to uncertainties about long-term treatment effectiveness being fully addressed, as the SDT arm had a short duration and long-term evidence is already available for TTD. Further and transparent collection of expert opinion may help in assessing the within health state responder resource use benefit, the applicability and real-world use of off-label TKIs as concomitant treatments in both treatment arms, and the applicability of dose escalation in UK clinical practice.

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Single Technology Appraisal

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis [ID6578]

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 Thursday 26 February 2026** 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 Uncertainty as to the population who would be eligible for avapritinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Decision problem Section 2.1, page 27: ISM-SAF availability needs updated.	Amend the sentence: ‘However, it appears that the ISM-SAF might not be used, which does not align with PIONEER, which creates some uncertainty as to how patients would be regarded as having moderate to severe symptoms for avapritinib.’ With the following: ‘However, ISM-SAF will be made available to UK clinical practice (as per commercial update from company) aligning with the PIONEER clinical trial, reducing some uncertainty as to how patients would be regarded as having inadequately controlled moderate to severe symptoms for avapritinib.’	This will accurately reflect the future landscape of ISM management in UK clinical practice. With the tool available, clinical practice will be closely aligned with the PIONEER clinical trial enabling more comprehensive definition of moderate-to-severe population. Since the submission in November 2025, the company has made the decision to make the ISM-SAF tool available to the NHS. ISM-SAF is specifically validated in patients with ISM and clinical practice, correlating with other patient-reported outcomes and representing a clinically meaningful endpoint for symptom severity burden in patients. With the availability of ISM-SAF in clinical practice, uncertainty of the patient population is significantly reduced.	Not a factual inaccuracy.

Decision problem Section 2.1, page 27: inaccurate statement about ISM-SAF and mild patients.	The following statement should be removed: '....some patients with mild disease according to the ISM-SAF might be eligible for clinical practice for avapritinib if the disease is affecting only one system.....'	Current statement contravenes marketing authorisation and patient population defined by ISM-SAF. As per clinical trial eligibility criteria, patients may be moderate to severe even if symptoms are only affecting one system. This protocol specifies the patient population is based on minimum mean TSS and ≥ 1 symptom in skin or GI domains of the ISM-SAF at baseline.	Not a factual inaccuracy. This is a definitional problem.
Decision problem Section 2.1, page 27: Incomplete UK clinical practice description.	Amend this sentence: 'In conclusion, it appears that in UK clinical practice patients will be chosen mostly according to the WHO criteria, which aligns with PIONEER.' With the following: 'In conclusion, it appears that in UK clinical practice patients will be chosen mostly according to the clinician-based judgement informed by WHO criteria, ISM-SAF (access to be granted by company), and objective measures of mast cell burden, which aligns with PIONEER.'	This accurately reflects how UK clinical practice was described by clinical experts as part of the model validation exercise.	Not a factual inaccuracy. This was only about the use of the WHO criteria.

Issue 3 Uncertainty as to the generalisability of SDT in the PIONEER trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 44, Section 3.2.4 Baseline characteristics of PIONEER trial and which clinical experts provided validation.	Amend part of the sentence: 'As can be seen there are discrepancies between PIONEER and the clinical experts.....' With the following: ' As can be seen there are discrepancies between PIONEER and the EAG clinical experts'	This amendment provides greater precision by clarifying that the discrepancies were identified through the specific clinical experts engaged by the EAG, which contrasted with the 3 clinical experts engaged by the company.	Not a factual inaccuracy. This applies to all clinical experts to some degree.

Issue 6 Appropriateness of using the ISM-SAF TSS to classify disease severity

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.2 Page 83: EAG reported a model structure as shown in Figure 4.1 appear differently compared to Figure 17 in CS.	Please amend this figure to align with Figure 17 in CS.	Figure 17 is validated by three UK clinical experts, and it will be more accurately reflect disease progression with arrows indicating the transition possibilities across three ISM health states and the progressions to the SSM and AdvSM.	Not a factual inaccuracy. Although different to CS Figure 17, the EAG preferred reporting the model structure as visualised in the company's economic model, which included relevant details (e.g. distinguishment between responders and

			non-responders) and was referenced accordingly.

Issue 7 Questionable generalisability of the company's modelled patient population to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.3 Page 85: missing detail of modelling mean starting age.	Revise the sentence: 'The modelled mean starting age (40 years) in the company's base-case is substantially lower than the mean age in PIONEER and the local EAG expert cohort (51 years).' With the following: 'The modelled mean starting age (40 years) in the company's base-case (validated by UK clinical experts) is substantially lower than the mean age in PIONEER and the local EAG expert cohort (51 years).'	While lower than the starting age of the PIONEER clinical trial, 40 years was established by UK clinical experts as a more representative of patients encountered in clinical practice.	Not a factual inaccuracy.

Issue 8 Likely under-estimation of avapritinib treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6 Page 89: The conversion of model cycles to weeks is incorrect.	Amend the following statement: "...a one-off discontinuation rate of ■■■ was applied in model cycle 3, i.e. at week 8." With the following: "...a one-off discontinuation rate of ■■■ was applied in model cycle 3, i.e. at week 12."	Statement corrected so that converted weeks to align with the corresponding 3 cycles One cycle equals 4 weeks (28 days), then Cycle 3 corresponds to 12 weeks instead of 8 weeks.	Corrected.
Section 4.2.6 Page 90: The description of the clinical expert input regarding the TSS reduction threshold is inconsistent with the "Clinical Expert Opinion Report" alongside CS.	Amend the paragraph: 'Clinical experts considered the 50% TSS reduction the "gold standard" but also considered that the 30% TSS reduction threshold may be sufficient, which was also highlighted by the ECNM-AIM consortium as a clinically significant response (clarification response B5.c) With the following: ' Clinical experts (n=3) considered the 30% TSS reduction sufficient as a clinically meaningful threshold for response to avapritinib aligning with ECNM-AIM recommendations (clarification response B5.c). A 50% TSS reduction is considered more conservative with one clinical expert describing this a 'gold standard' based on their clinical experience.'	The current statement misinterprets the clinical expert engagement report which including the following insights: a) One clinical expert has a strong opinion and stated 50% TSS reduction as the "gold standard" based on his/her own clinical experience. But all three clinical experts confirmed and agreed 30% decrease in TSS would be sufficient to continue treatment with avapritinib. b) In CS reference pack "Clinical Expert Opinion Report" Q5.c., UK clinical experts confirmed the 30%	Suggestion implemented.

		TSS improvement is sufficient.	

Section 4.2.6, Page 90: The description misinterprets Table 29 in the company's clarification response.	In the EAG report, the following is stated: 'Table 29 of the company's clarification response showed that at week 24, approximately █ of patients in PIONEER were still on treatment, while in the company's model it is only approximately █ (see also K-M curve in Figure 1 of the clarification response)...' With the following: 'Table 29 indicates that, following the week-24 assessment, approximately █ of patients were classified as avapritinib responders (based on a $\geq 30\%$ TSS reduction threshold), with patients distributed across three ISM health states accordingly. However, Figure 1 (K-M curves) suggests that approximately █ of patients in PIONEER remained on treatment at around week 24.'	Agree on the value discrepancy of time-on-treatment identified by the EAG; this discrepancy occurred due to the level of data used in K-M curve generation. Table 29 in the company's clarification response did not reflect █ of patients still on treatment at week-24. Instead, Table 29 in the clarification response presents the health state distribution for ISM patients still on treatment, but this only presents the proportion of patients spread across the three severity levels of disease. This severity distribution data did not represent the proportion of patients still on treatment. Approximately █ discontinuation of the treatment was based on the model assumption using 30% TSS reduction threshold, while this does not conflict with or against the result in the PIONEER trial, as the trial did not have a stopping rule based on the TSS improvement.	Amended to refer to Figure 1.

		The discontinuation in PIONEER was mainly led by the safety concerns or the patient's own choice, treatment non-responders are still considered during the trial period. Thus, a significant value discrepancy [REDACTED] has shown in the KM curve compared with the model assumption.'	

Issue 10 Progression to SSM and AdvSM

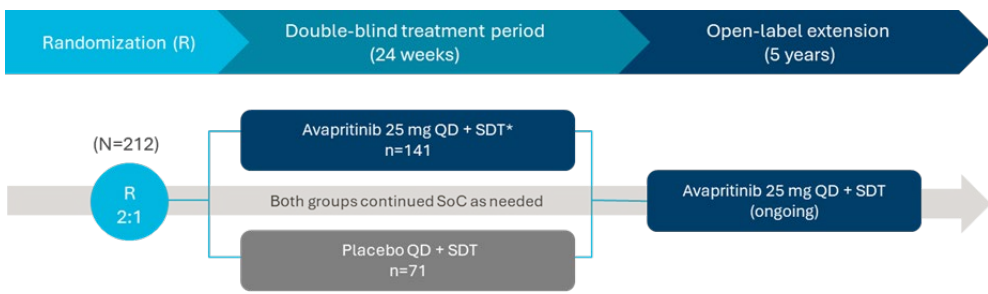
Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Section 4.2.6, under EAG comment e) states "...referencing to wrong cells on the Distributions sheet (e.g. cell AG); ..." (Page 93) The description is inconsistent with the updated model (company's clarification response) and the original model (CS).	Please indicate the exact location of this error, as the company did not observe this wrong cell reference in the updated company model with a clarification response. Company checked "Distribution!AG" in "TSS" sheet, no results were found.	The current statement lacks transparency and details. The description of the error was not found in the models.	This was indeed unclear in the EAG report, and more detail has been added.
Section 4.2.6, Page 93	Amend the statement "...mortality in the SSM state not being accounted for:"	The current statement does not acknowledge the formulae applied to the model for	Amended.

The description is inconsistent with the updated model (company's clarification response) and the original model (CS).	Please amend this sentence, as the mortality in the SSM state was accounted in the Sheet "TSS", Column AC and Column AO. A minimal small value appears when decimals are increased in these two columns. The SSM mortality for the avapritinib arm starts from cycle 7 (after 24-week initial TSS assessment), and for the SDT arm from cycle 2.	accounting for SSM mortality. The starting cycle was applied differently for the avapritinib arm and the SDT arm reflected the treatment effects compared to the SDT and avapritinib, where patients who stay in the avapritinib treatment arm potential has better disease control and no mortality due to progression to SSM or AdvSM was observed in the initial 24-week assessment in the PIONEER trial.	

Additional inaccuracies: PIONEER clinical trial details and efficacy

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.2 Page 36: Summary of details of PIONEER trial.	Amend the sentence: 'The second part was the pivotal randomised, double-blind, placebo-controlled trial with a 2:1 randomisation ratio (avapritinib).' With the following: 'The second part was the pivotal randomised, double-blind, placebo-controlled trial with a 2:1 randomisation ratio (avapritinib 25 mg + SDT to placebo + SDT)'	While 141 patients received avapritinib and 71 received placebo (confirming a 2:1 ratio), providing only the intervention name in the brackets is mathematically	Corrected.

		incomplete for defining a ratio arm and can lead to ambiguity regarding the study's control group.	
Section 3.2.9.3 Page 73: Part 3 open-label extension phase safety results AE mis-reporting.	Amend the sentence: 'The company also reported that avapritinib demonstrated a consistent safety profile across analysis populations, with the most frequently reported AEs ($\geq 10\%$ of the safety population) including COVID-19 (██████████), diarrhoea...' With ' The company also reported that avapritinib demonstrated a consistent safety profile across analysis populations, with the most frequently reported AEs ($\geq 10\%$ of the safety population) including COVID-19 (██████████), diarrhoea...'	This amendment corrects a factual error where the percentages for 'Any AE' (████% to █████%) were mistakenly attributed to COVID-19, ensuring the narrative accurately reflects the specific incidence data provided in Table 35 of the dossier and Table 3.32 in the EAG report: AEs that occurred in $\geq 10\%$ of the PIONEER safety population (avapritinib, all starting doses) at DCO	Corrected.
Section 3.6 Page 78: Conclusions of the	Amend the sentence 'The EAG noted that there are discrepancies between PIONEER and the clinical experts in the percentage use of each kind of SDT...'	This amendment provides greater precision by clarifying	Not a factual inaccuracy.

clinical effectiveness section.	With: 'The EAG noted that there are discrepancies between PIONEER and the EAG clinical experts in the percentage use of each kind of SDT...'	that the discrepancies were identified through the specific clinical experts engaged by the EAG	
Section 3.6 Page 78: Conclusions of the clinical effectiveness section.	Amend the sentence '... inhibitor (montelukast), corticosteroid (prednisolone), cromolyn sodium, omalizumab and loperamide).'	This amendment clarifies that anti-diarrhoeal medication was omitted from the clinical and economic evaluations	Not a factual inaccuracy.
Figure 3.1 Page 36: abbreviations	Remove "SLRs = systematic literature reviews" from the list of abbreviations.	Abbreviation is not used in the corresponding figure.	Corrected.
Figure 3.2 Page 37: abbreviations	Replace Figure 3.2: PIONEER Phase 2 trial study design:  With the following amended figure:	SDT terminology aligned in figure of Phase 2 trial study design to improve clarity of SDT treatments used ubiquitously in patients with ISM.	Amended.

	Randomization (R) Double-blind treatment period (24 weeks) Open-label extension (5 years) (N=212) R 2:1 AYVAKIT 25 mg QD + SDT* n=141 Both groups continued SDT as needed Placebo QD + SDT n=71 AYVAKIT 25 mg QD + SDT (ongoing)		
Figure 3.2 Page 37: abbreviations list	Remove 'SAF = Symptom Assessment Form' from the list of abbreviations	Abbreviation is not used in the corresponding figure.	Corrected.
Table 3.6 Page 44: Demographic and baseline characteristics of PIONEER participants in Europe and the UK, list of abbreviations	Remove 'PCR = polymerase chain reaction' from the list of abbreviations	Abbreviation is not used in the corresponding table.	Amended.
Table 3.10 Page 49: Quantitative comparison of efficacy outcomes in PIONEER Part 1, list of abbreviations	Remove 'C4D1 = Cycle 4 Day 1; C7D1 = Cycle 7 Day 1' from the list of abbreviations	Abbreviations are not used in the corresponding table.	Corrected.

Additional inaccuracies: Cost effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 5.1 Page 101: value presented in the EAG report is inconsistent with the CS: The ICER(£/QALY) presented in the Table 5.2 is also inconsistent with the data reported in the CS.	Amend the sentence: “Overall, the technology is modelled to affect costs by: • Increased drug acquisitions costs of avapritinib (██████, █████ the total decreased costs) • Decreased drug acquisitions costs of SDT █████ the total decreased costs)” With the following: “Overall, the technology is modelled to affect costs by: • Increased drug acquisitions costs of avapritinib (██████: • Decreased drug acquisitions costs of SDT █████: • ICER(£/QALY) reported in the CS is █████.”	The current statement misreported the value presented in the CS.	Corrected
Section 5.1, Page 103: Sources of utility for ISM, SSM, and AdvSM mis-reported.	Amend the partially correct sentence: “Clinical effectiveness, health state occupancy and utility input parameters were derived from trials (particularly PIONEER)...” is partially correct. With the following: the sources of utility for ISM, SSM and AdvSM.	The utility values applied to the model were sourced from and informed by different trials and study reports.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	"ISM patient clinical effectiveness, health state occupancy, and utility input parameters were derived from PIONEER trial, SSM and AdvSM are estimated from Dutch Expert advisory board and PATHFINDER trial data (AdvSM progressed 1L)."		

Additional inaccuracies: Critique of the methods of systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.1.1 Page 31: Searches: Incomplete description.	Amend the sentence: 'Appendix B of the CS ¹⁰ details the systematic literature review (SLR) conducted to identify relevant clinical evidence for the use of avapritinib for treating inadequately controlled moderate to severe ISM.' With the following: Appendix B of the CS ¹⁰ details the systematic literature review (SLR) conducted to identify relevant clinical evidence for the use of avapritinib and comparator treatments for treating inadequately controlled moderate to severe ISM.'	More accurately reflects what the searches were designed to identify, namely clinical evidence of avapritinib and comparator therapies in the target patient population.	Not a factual inaccuracy.
Section 3.1.2 Page 31: Inclusion criteria: Incomplete description.	Amend the sentence: 'Additionally, the comparator listed on Table 3.1 for the evidence eligibility criteria lists 'best	Inclusion of full criteria for comparators shows that any relevant studies would be included in the SLR (including	Not a factual inaccuracy.

	supportive care’ and emphasises that this is ‘author defined’. With the following: ‘Additionally, the comparator listed on Table 3.1 for the evidence eligibility criteria lists ‘best supportive care’ and emphasises that this is ‘author defined’ as well as any other pharmacological/ non-pharmacological intervention. Exclusion criteria is set to none.’	those treatments listed as intervention other than avapritinib).	
Section 3.1.2 Page 31: Inclusion criteria, Table 3.1: Incorrect placement of therapy in TKI basket.	Revise ‘Intervention’ inclusion criteria cell by removal of ‘Immunoglobulin’ from bulleted list of ‘Other TKIs including:’ Include as a separate subheading underneath TKI list.	This will improve the accuracy of treatments included as interventions in this review.	Amended.

Additional inaccuracies: Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Statement of DP Page 16: Incorrect numbered heading.	Numbered heading ‘2.1’ included without any accompanying text before a section break. Please remove to correct numbering in document.	Typographical error.	Can’t find this.
Section 2.4 Page 29 Comparators Line 9: Punctuation missing.	Amend the sentence: ‘Finally, she stated that interferon-alpha, cladribine, and TKIs: ³ <i>“would be regarded as disease modifying –</i>	Typographical error.	This is a direct quote.

	<i>aimed at decreasing the mast cell burden not just controlling symptoms'</i> Please add a full stop at the end of sentence.		
Section 2.4 Page 29 Comparators, Line 13: Incorrect spacing.	Amend the sentence: 'This indicates that omalizumab would be included as SDT, but according to Figure 11 in the CS.....' With the following: 'This indicates that omalizumab would be included as SDT, but according to Figure 11 in the CS....'	Typographical error.	Corrected.
Section 3.1.2 Page 31 Inclusion criteria, end of paragraph: Incorrect spacing.	Amend the following sentence: '.....it is feasible that the eligibility criteria and screening process may not have identified relevant studies through error, definition misalignment, or uncertainty.' Remove spacing before full stop.	Typographical error.	Corrected.
Section 3.1.2 Page 31 Inclusion criteria, Table 3.1: Incorrect punctuation and placement in list of outcomes.	Outcomes list should all be bulleted under 'Efficacy' sub-heading including HRQoL/PRO in this list; safety should be included as separate subheading as follows:	Typographical error.	Amended.

	Efficacy • Change in ISM-SAF TSS, • Change in serum tryptase levels • Change in KIT D816V VAF • Change in BM MC aggregates: • Change in BM MC • Proportion of patients with a $\geq 50\%$ reduction in BM MCs or no aggregates for patients with aggregates at baseline • Change in BSC concomitant medication usage • ORR (including complete and partial remission and their definitions) • DoR • HRQoL changes: MC-QoL, MSAF, PGIS, SF-12, PGIC, EQ-5D, MS2D2 Safety • AEs • SAEs • Study/treatment discontinuation • Discontinuation due to AEs		
Section 3.1.3 Page 34 Critique of screening and data extraction, Lines 2-5: punctuation errors.	Revise the paragraph: 'The company state in Appendix B of the CS¹ that level 1 screening was performed by two independent NHTA reviewers who reviewed each reference identified in the literature search, applied basic study selection criteria and included or excluded the record. They state that uncertainties regarding the inclusion of studies was checked by a third reviewer.'	Typographical errors.	Corrected.

	With the following: 'The company state in Appendix B of the CS ¹ that level 1 screening was performed by two independent NHTA reviewers who reviewed each reference identified in the literature search, applied basic study selection criteria and included or excluded the record. They state that uncertainties regarding the inclusion of studies was checked by a third reviewer.'		
Section 3.2.3 Page 40 Statistical analysis of PIONEER trial, Line 12	Replace 'vesus' with 'versus'	Typographical error	Corrected.
Figure 3.3 Page 42: CONSORT diagram of PIONEER clinical study participants, list of abbreviations	Replace ' CONsolidated' with 'Consolidated'	Typographical error	Not a factual inaccuracy.
Table 3.7 Page 45: Symptom-directed treatment basket	Add '%' signage to the numbers in rows 1,2, columns 7,8 Replace '...due to it associated safety risk.' With '...due to its associated safety risk.' in row 2, column 5 Replace signage „ with " in row 5, columns 7,8	Typographical and grammatical errors	Amended.

	Replace 'One clinical expert thought that Nalcrom possibly have a usage of around █████%...' With 'One clinical expert thought that Nalcrom possibly has a usage of around █████%...'		
Table 3.8 Page 48: Mean change in ISM-SAF TSS from baseline to week 24 (PIONEER Part 1 ITT Population), list of abbreviations	Replace 'SAS' with 'SAF'	Typographical error	Corrected.
Page 48 EAG comment, Line 4	Replace 'Table 3.7' with 'Table 3.8' Replace 'Table 3.8' with 'Table 3.9'	Typographical errors	Corrected.
Page 49 EAG comment, Lines 5-6	Amend ' Further details of week 24 results can be found Table 3.10.' With ' Further details of week 24 results can be found in Table 3.10.'	Typographical error.	Corrected.
Page 56 EAG comment, Line 20	Amend '... achieving both $\geq 30\%$ $\geq 50\%$ reduction in TSS' With '... achieving both $\geq 30\%$ and $\geq 50\%$ reduction in TSS'	Typographical error.	Corrected.
Page 57 EAG comment, paragraph 2, Lines 12-13	Amend 'Further details can be found in Table 18 of the clarification letter response, but they...' With 'Further details can be found in Table 17 of the clarification letter response, but they...'	Typographical error.	Corrected.

Section 4.1.1 Page 80: Uppercase used for final word in section heading, Line 3.	Replace the section subheading '4.1.1 Searches performed for cost effectiveness Section' With the following: '4.1.1 Searches performed for cost effectiveness section'	Typographical error.	Corrected.
Section 4.1.1 Page 80, final bullet point, Lines 37-39	Revise latter part of sentence: ' <i>...the strategies are designed to find HRQoL studies, so the EAG are sure if this is a typographical error.</i> ' With the following: ' <i>...the strategies are designed to find HRQoL studies, the company has confirmed this is a typographical error.</i> '	Typographical error.	Amended.
Section 4.2.3 Page 85 Line 11: under EAG comment bulletin point a) Terminology spelling mistake.	Replace terminology in the sentence: ' <i>However, the EAG's clinical expert noted that the IAM-SAF threshold (i.e. TSS ≥ 28)...</i> ' With the following: ' <i>However, the EAG's clinical expert noted that the ISM-SAF threshold (i.e. TSS ≥ 28)...</i> '	Typographical error.	Corrected.
Section 4.2.6 Page 91 Lines 42-43: under EAG comment bulletin point c), grammar error.	Replace the latter part of the starting sentence of this paragraph: '... SDT long-term effectiveness assumed to be equal to baseline:...' With the following: '... SDT long-term effectiveness is assumed to be equal to baseline:...' "	Grammar error.	Not an error.
Section 4.2.6 Page 93 Line 18: under EAG comment bulletin point g), punctuation errors.	Remove the duplicated colons: 'The company's response was contradictory::' Change to the following: 'The company's response was contradictory.'	Typographical errors.	Corrected.

Section 4.2.7 Page 94 Line 7: AEs, grammar error.	Missing descriptive nouns'...with higher incidence assumed under SDT ...' Amendment with the following '...with a higher incidence assumed under SDT ...'	Typographical error.	Not an error.
Section 4.2.8.3 Page 95 Line 30: under EAG comment bulletin point b), abbreviation errors.	Replace the abbreviation : 'Cross-sectional ordinary least squares (LSs)'. With the following: 'Cross-sectional ordinary least square (LS)'	Typographical errors.	Corrected.
Section 4.2.8 Page 96 Lines 1-2: under EAG comment bulletin point b), grammar error.	Missing descriptive nouns: 'As sensitivity analysis, Last Observation Carried Forward (LOCF) was used. ...' Amendment with the following "As a sensitivity analysis, Last Observation Carried Forward (LOCF) was used..."	Typographical error.	Corrected.
Section 4.2.10 Page 99 Lines 36-37: reference to the wrong tables.	Replace the sentence cited the table in the paragraph; '... a proportional shortfall of 44.69% (see Table 4.6). Hence, a severity modifier of x1.0 was applied (see Table 4.7).' With the following: '... a proportional shortfall of 44.69% (see Table 4.7). Hence, a severity modifier of x1.0 was applied (see Table 4.6).'	Table reference errors.	Corrected.

Section 5.3.3 Page 103 Line 19: wording “cross validation” is missing a punctuation.	Replace the sentence: ‘to support meaningful cross validation of the company’s economic model for avapritinib in ISM.’ With the following: ‘to support meaningful cross-validation of the company’s economic model for avapritinib in ISM.’	Typographical errors.	Amended.
Section 5.3.4 Page 103 Line 36-37: under EAG comment bulletin point a), grammar error.	Replace the sentence: ‘the EAG requested completing the TECHnical VERification (TECH-VER) checklist and provide the results in its clarification letter.’ With the following: ‘the EAG requested completing the TECHnical VERification (TECH-VER) checklist and providing the results in its clarification letter.’	Typographical error.	Corrected.
Section 6.4 Page 113 Line 18: duplicated sentence.	Remove the first row of the second paragraph of this section: ‘Important uncertainties were observed in the company’s modelling of treatment effectiveness: first, the’	Typographical errors.	Corrected.

Additional inaccuracies: Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
EAG report, page 13, line 2 (Table 1.3. Key Issue 2) + page 28, line 32-34	Safety data for PIONEER Part 1 and Part 3 are confidential.	Safety data to be marked as follows:	Amended.

		'There was a [REDACTED] grade 3 reaction rate with 50mg, rising to [REDACTED] with 100mg.....'	
EAG report, page 57, line 24; page 58, line 1	Data on file for PIONEER Part 3 long-term efficacy, originally confidentially marked in CS.	Confidential long-term efficacy data to be marked as follows: 'Mean (SD) reductions from baseline in TSS were [REDACTED] points at 1 year, with sustained reductions of [REDACTED] points at 2 years and [REDACTED] points at 3 years.'	Amended.
EAG report, page 70, line 21-23	Data on file for PIONEER Part 2 subgroup analysis is unpublished and was originally marked as confidential in CS.	Data on file from PIONEER Part 2 subgroup analysis to be confidentially marked as follows: 'Baseline serum tryptase level also appeared to influence treatment response, with a MD of [REDACTED] points in patients with <20 ng/mL compared with - [REDACTED] points in those with ≥20 ng/mL. The subgroup with baseline serum tryptase <20 ng/mL was small (placebo n=14; avapritinib n=[REDACTED]). ¹	Amended.
EAG report, page 71, line 2-5	PIONEER Part 1 safety results are data on file and originally confidentially marked in the CS.	Safety data from PIONEER Part 1 is confidential and the marking is as follows:	Amended.

		‘Cognitive effect AEs included cognitive disorder and memory impairment, reported in [REDACTED] each in the 25 mg and 100 mg groups, respectively, and a serious adverse event (SAE) of delirium in [REDACTED] in the 50 mg group. Most cognitive events were non-serious and Grade 1 or 2; [REDACTED] was Grade 3 and led to treatment discontinuation.’	
EAG report, page 73, line 9-11	Data on file for PIONEER Part 3 long-term safety and adverse event profiles was originally confidentially marked in CS.	Safety data from unpublished PIONEER Part 3 reported in text, as with tabular data, should be marked as follows: ‘.....AE profiles were comparable between participants who initiated avapritinib at 25 mg ([REDACTED]) and those who initiated treatment at any dose ([REDACTED]).....’	Amended.
EAG report, page 75, line 5	PIONEER Part 1 safety results are data on file and originally confidentially marked in the CS.	Safety data from PIONEER Part 1 is confidential and the amended marking is as follows: ‘In Part 1, [REDACTED] SAE of delirium was reported in the avapritinib 50 mg group.....’	Amended.

EAG report, page 75, line 12	SAEs reported in the PIONEER safety population (avapritinib all starting doses) at latest data-cutoff is confidential.	As per Table 3.33 in EAG report, SAEs are to be marked confidential as follows: 'The company also reported SAEs of [REDACTED] (ranging from [REDACTED] % to [REDACTED] %)...'	
EAG report, page 76, line 6-8	Anaphylaxis reported in PIONEER Part 2 is confidential.	Adverse events, namely anaphylaxis, are to be marked as follows: 'At baseline, [REDACTED] patients in the 25 mg avapritinib group and none in the placebo group had anaphylaxis that required epinephrine treatment. Post-baseline, [REDACTED] patients in the 25 mg avapritinib group.....'	Amended.
EAG report, page 76, line 12-14	Anaphylaxis reported in PIONEER Part 2 is confidential.	Adverse events, namely anaphylaxis, are to be marked as follows: 'Exploratory analyses revealed a reduction of anaphylaxis frequency with avapritinib treatment, [REDACTED] of patients who had baseline anaphylaxis (N=[REDACTED]) experienced no post-baseline events during the 24-week treatment period, compared to all placebo patients (N=[REDACTED])....'	Amended.

EAG report, page 88, line 9, 11, 15, 16	Duration of treatment and inputs used for this calculation for avapritinib is confidential.	Data and inputs related to duration of treatment is confidential, amended marking as follows: Line 9: 'The initial response criterion used by the company led to ■■■ of patients continuing avapritinib treatment.' Line 11: 'The RWE cohort included ■■ SM....' Line 15: '.....mean duration of treatment (DoT) of ■■ years...' Line 16: '...■■■ of patients in the avapritinib....' Line 30: 'At ■■ years, all patients remaining.....'	Amended.
EAG report, page 91, line 1	Estimated duration of treatment for avapritinib is confidential.	As before in CS and clarification responses, duration of treatment is confidential as follows: 'This resulted in the company's estimate of ■■ years.'	Amended.

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

Avapritinib for treating uncontrolled moderate to severe indolent systemic mastocytosis

Topic ID:

6578

Managed Access Lead:

Milena Wobbe

Date of assessment(s):

02/03/2026

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	Rationale for rating	To consider managed access, a committee will need a managed access proposal, along with a feasibility assessment from the NICE managed access team. Currently no managed access proposal has been submitted. The managed access team should be contacted if a managed access proposal is expected to be requested or submitted at a later point in the NICE evaluation process.
	Previous ratings and rationale for change	N/A

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	As there is no proposal, this can only enter CDF if a proposal is received after the first committee meeting.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, though no proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	Low	The uncertainties relate to modelling queries that need resolving. SACT comparator data might be useful to request. However, this should happen before the committee meeting and feed into the discussion to aid committee decision making.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	Whilst data sources are available, it is unlikely to be meaningful for managed access.

Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Medium	Whilst data collection is feasible, the appropriateness is unclear.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered	
1	N/A

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	N/A