National Institute for Health and Care Excellence

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Blueprint Medicines (company)	With no targeted, disease-modifying therapy approved for indolent systemic mastocytosis (ISM) in NHS clinical practice, there is a therapeutic unmet need in patients due to the substantial symptom burden. Patients with moderate-to-severe disease face symptoms which are not adequately controlled with best supportive care (BSC) and off-label treatments used in current NHS practice. Clinical guidance for SM (including ISM) is based on an individualised treatment approach for ISM due to its heterogeneity and the significant burden of symptoms stemming from skin involvement (e.g. pruritus, flushing), gastrointestinal (GI) issues, osteoporosis and/or anaphylaxis.[1-3] While no specific UK clinical guidance is available for ISM, clinicians refer to European and US guidelines.[4] European ECNM-AIM guidelines recommend first-line BSC therapeutic options for the previously mentioned major symptom areas.[5,6] Meanwhile, National Comprehensive Cancer Network (NCCN) SM guidelines recommend administration of anti-mediator drug therapy for symptomatic ISM with mast cell activation symptoms.[7]	Thank you for your comments. No action needed.

Section	Stakeholder	Comments [sic]	Action
		Further, avapritinib (if platelet counts are ≥50 × 109/L) is listed as a preferred option (as per Food and Drug Administration approval), 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.[7] This heterogeneous disease exhibits a broad symptom profile with varying degrees of severity (mild, moderate or severe) and types (skin, gastrointestinal, osteoporosis, and anaphylaxis). Currently, BSC is based on symptomatic relief and does not address the underlying pathophysiology which increases the likelihood of symptom persistence or escalation.[8,9] Progression from ISM to more advanced forms (including advanced systemic mastocytosis [AdvSM]) is linked to elevated tryptase, levels of *KIT D816V* mutation in peripheral blood, and high symptom burden.[10-12] A US study (n=2,706) (Mukherjee et al., 2023) found 4.4% of high-burden patients progressed, and 15% with mild symptoms worsened within two years. Poor symptom control increases progression risk and ultimately risk of death.[13] With no disease-modifying therapies for ISM approved by NICE up until now, patients inadequately controlled with BSC symptomatic therapies may progress to more advanced forms of mastocytosis representing a substantial unmet need. With approval and reimbursement of avapritinib for AdvSM (since 2024)[14], Blueprint Medicines believe that standard technology assessment (STA) of this novel tyrosine kinase inhibitor (TKI) in ISM is warranted especially as this population constitutes a majority of SM patients with substantial symptom burden. This coupled with the potential of progression to more advanced forms of SM (such as AdvSM), in the absence of a targeted therapy, necessitates patient access and justify this evaluation.[13,15]	

Section	Stakeholder	Comments [sic]	Action
	British Association of Dermatologists	We agree that a Single Technology Appraisal (STA) is appropriate for evaluating avapritinib for moderate to severe indolent systemic mastocytosis. This condition represents a significant unmet need for novel treatments in adult indolent systemic mastocytosis, as current standard of care treatments offer limited effectiveness and do not improve the appearance of the skin lesions. This is an underrated cause of psychological distress. Indolent systemic mastocytosis may also cause severe systemic effects on bone density (osteopenia or osteoporosis), neurocognitive symptoms, allergies (anaphylaxis) and risk of progression to smouldering and advanced disease. The evaluation of avapritinib is, therefore, an important milestone in advancing the management of this multisystem clonal mast cell disorder that often presents initially to dermatologists with skin lesions.	Thank you for your comments. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care	We view this evaluation as entirely appropriate because avapritinib has been shown in trials and in use in other countries where it has already received regulatory approval to improve the quality of life of people with moderate to severe indolent systemic mastocytosis (ISM). It is the first treatment for ISM that is disease modifying. Avaprintinib reduces the burden of mast cells in the bone marrow, decreases tryptase (a key marker used to measure mast cell burden), and improves quality of life using a reasonable assessment tool. These benefits are evident in the Pioneer trial and the drug has been in use outside of trials in the US since May 2023 and in Europe since December 2023. In addition, though we can't know yet whether avapritinib prevents progression to more advanced forms of systemic mastocytosis, there is a plausible mechanism by which it could. While we agree that avapritinib should be assessed through the STA process given the current criteria for assigning the assessment route, we note that	Thank you for your comments. No action needed.

Section	Stakeholder	Comments [sic]	Action
		STA is ill-suited to rare disease medications where the trial cohorts are relatively small.	
	British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)	The evaluation is appropriate	Thank you for your comment. No action needed.
Wording	Blueprint Medicines (company)	The wording of the draft remit should be correct and aligned with the anticipated marketing authorisation (as per European Medicines Agency [EMA] reference): [redacted]. [16]	We have updated the remit to refer to inadequately controlled moderate to severe indolent systemic mastocytosis
	British Association of Dermatologists	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care	Yes, this looks correct.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
	Immunology Professional Network		
Timing issues	Blueprint Medicines (company)	As mentioned previously, current NHS clinical practice of BSC and off-label treatments do not address the underlying pathophysiology of ISM.[17] Avapritinib represents a step-change in the treatment of patients with ISM, with its disease-modifying action as a highly selective and potent TKI targeting the *KIT D816V* mutation, the underlying driver of ISM in ~95% of patients.[12,18,19] With avapritinib treatment, symptom and mast cell burden are reduced (as shown by the pivotal PIONEER clinical trial NCT03731260) compared to placebo over 6 months and sustained in the ongoing open-label extension (OLE).[20,21] Additionally, health-related quality of life (HRQoL), which is markedly impacted in patients with ISM, is improved with avapritinib reflecting the potential for this agent to achieve not only symptom control but also alter patients' daily lives. With approval and reimbursement in other mastocytosis indications, this appraisal will address substantial unmet need in moderate-to-severe patients with ISM by targeting the underlying pathophysiology thus curtailing progression to more advanced forms of disease.	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.
	British Association of Dermatologists	There is a clear unmet need for novel and effective targeted treatment for this condition, as such this appraisal is welcome.	Thank you for your comment. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.

Section	Stakeholder	Comments [sic]	Action
	British Society for Immunology Clinical Immunology Professional Network	Urgent (see below) There are no current treatments to moderate disease burden in indolent macrocytosis, merely treatments that directed at symptom control. This should be considered when looking at 'comparators'.	Thank you for your comments. This topic has been scheduled into the work programme and NICE aims to provide timely guidance to the NHS.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Blueprint Medicines (company)	**Pathophysiology** Information is sparse around further detail suggested on the pathophysiology of ISM in patients, include the following wording: *KIT D816V mutation is typically present in approximately 95% of ISM cases and this leads to greater disease activity. This is coupled with uncontrolled proliferation and activation of mast cells.*[12,18,19] **Symptom burden impact on health-related quality of life (HRQoL)** Blueprint Medicines noted the omission of HRQoL in the introductory background section. This is a major part of the disease impact on patients and is also included as a secondary outcome in the pivotal clinical trial. The company suggests addition of the following text to capture this important aspect of ISM: *The constellation of symptoms exhibited by people living with ISM, particularly in the moderate-to-severe spectrum, leads to a significant reduction in HRQoL according to studies in Europe and US.*[22,23] *A substantial*	We have added the prevalence of the KIT D816V mutation. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. Health-related quality of life effects are implicit in the description of symptoms. Effects on health related quality of

Section	Consultee/ Commentator	Comments [sic]	Action
		proportion of patients reported that they had to reduce their work hours,[23-26] that they were impaired in performing activities of daily living,[24,27] and that the symptoms of ISM interfered with their social relationships.[27]	life will be described and quantified in more detail during the appraisal process.
		Prevalence Additionally, Blueprint Medicines suggests replacement of the prevalence estimation with one specific for ISM, not just for systemic mastocytosis. Proposed wording is as follows: *ISM is the most common subtype of SM, accounting for approximately 90% of adult SM cases in the UK and globally. While detailed data on the prevalence of ISM in the UK is not available, clinical experts as part of the UK Mastocytosis Support Group estimate 1 in 10,000 people .[28] Mirroring the broader European Perceptions, Realities, and Insights on SM (PRISM) survey cohort, 67% of UK patients (total n=50) were classified as moderate-to-severe, the most prevalent subpopulation.[25,29]* *Other country prevalence estimates of ISM can be used as a reference in lieu of UK data, for instance, the CEREMAST study conducted in France reported 4,269 patients with ISM (including those with skin mastocytosis).[30] In terms of symptom severity, 53% (n=2,257) had moderate-to-severe disease with 36% not adequately controlled with symptomatic treatment.[30]* Also, Blueprint Medicines would like to highlight that the NHS reference for treatment of mastocytosis included in the draft scope is not entirely appropriate. This NHS information regarding ISM is mixed with other mastocytosis conditions thus it is unclear which information is specific for ISM patients.[31] The company suggest replacing this source with references	We have updated the prevalence figure to the estimate for ISM. We have not added further detail as the background section aims to be a brief summary and is not designed to be exhaustive. The background section has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		regarding centre of excellence cohort experience including: Oni et al. (2019)[32] and Veitch et al. (2023)[33]. **Technology** As before in remit, amend wording around marketing authorisation for patients inadequately controlled by symptomatic treatment. Also, Blueprint Medicines suggests amendment of wording regarding marketing authorisation in other indications: *Avapritinib's current marketing authorisation is for unresectable or metastatic gastrointestinal stromal tumour (GIST), or AdvSM including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).* As a key part of the background section in the draft scope, the nature of avapritinib as a disease-modifying treatment for ISM should be clearly communicated. Blueprint Medicines advises the addition of the following paragraph to reflect this: *Avapritinib in ISM is considered to be disease-modifying as it has a high affinity for the underlying KIT D816V mutation, a common driver of this rare mast cell disease.[34] Avapritinib's sustained ability to reduce mast cell burden, improve symptoms and patient HRQoL in the PIONEER trial is strongly indicative of a disease-modifying effect, especially with long-term clinical efficacy reported up to 3 years.[20,35-37]*	We have updated the wording to refer to inadequately controlled moderate to severe indolent systemic mastocytosis This section is intended to describe only current marketing authorisation status and ongoing or completed clinical trials.
	British Association of Dermatologists	Non-sedating second generation antihistamines are the mainstay of treatment for control of itching and flushing in the skin and are used in anaphylaxis.	We have updated the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
		They may have some additional benefits for gastrointestinal symptoms and neurocognitive symptoms. Additional anti-mast cell therapies may include H2 antihistamines and montelukast. Phototherapy and photochemotherapy (PUVA) may provide additional control of skin symptoms and a temporary improvement in the appearance of the lesions which is not sustained on stopping. Phototherapy cannot be maintained long term because of the risk of promoting skin cancers and skin ageing. Sodium cromoglicate is primarily used for mast cell related bowel symptoms because it is poorly absorbed. Oral corticosteroids are not used for indolent systemic mastocytosis except in very rare instances, such as highly unstable and hard to control recurrent anaphylaxis. Therefore, they are not a valid comparator.	
	British Society for Allergy and Clinical Immunology	The information given is accurate, although I would amend the last paragraph to say, “Treatment aims to relieve symptoms and includes antihistamines, leukotriene inhibitors, and occasionally corticosteroids.”	We have updated the background section.
	The UK Mastocytosis Support Group and Leukaemia Care	We have several places where we think the background information could be improved: The KIT mutation, ~~makes the mast cells more sensitive to the effects of a signalling protein called stem cell factor (SCF). SCF plays an important role in stimulating the production and survival of certain cells, such as blood cells and mast cells, inside the bone marrow.~~ **~~Error! Reference source not found.~~** which affects the structure of a receptor on the mast cell’s membrane, causes mast cells to proliferate in the absence of stem cell factor, the ligand that normally stimulates production of new mast cells. This means that too many mast cells are produced. The mutation can also lead to prolonged survival of	We have updated the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
		these mast cells. Together these two effects of the mutation lead to the accumulation of excess mast cells in the body's tissues, where they normally play a role in immune defense. 1. The mast cells release large amounts of histamine and numerous other mediators into the blood; having too many mast cells in ISM causes symptoms such as skin rash, itchy skin, hot flushes, blood pressure changes, fainting, tachycardia, headache, vomiting, diarrhoea, trouble with cognition and memory, ~~organ failure~~ and anaphylaxis. [Organ failure occurs in advanced forms of SM, not in indolent SM.] Patients can present with some of all of these symptoms, which may be mild or severe, and the symptoms may be episodic or chronic, and may arise unpredictably. 2. There are 2 main types of mastocytosis, cutaneous mastocytosis, which affects the skin (mainly in children), and systemic mastocytosis, which affects the skin, internal organs and bones (mainly in adults). Systemic mastocytosis has subtypes defined by level of disease: indolent (the most common, about 90% of cases**Error! Reference source not found.**), smouldering, and advanced systemic mastocytosis. For most people, symptoms of indolent systemic mastocytosis are mild to moderate, but vary from person to person. ~~In 1% to 3% of people, indolent systemic mastocytosis can progress to a more aggressive form.~~**Error! Reference source not found.** A recent study using the largest available data set on indolent systemic mastocytosis, 4.9% of ISM patients progressed to more advanced types. (Trizuljak J, Sperr WR, Nekvindová L, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy. 2020 Aug;75(8):1927-1938.) 3. Current treatment aims to relieve symptoms and prevent anaphylaxis and includes H1 and H2 type antihistamines, anti-leukotriene medications,	

Section	Consultee/ Commentator	Comments [sic]	Action
		sodium cromoglicate, oral corticosteroids and transient treatments to manage skin symptoms. Treatment also aims to prevent or limit osteoporosis. 4. Indolent systemic mastocytosis typically affects both men and women equally and the onset is generally during working age, between ages 20 and 40 (in contrast to advanced SM which tends to start later). (Siebenhaar, F., Brehler, R., Christen, D. *et al.* Mastocytosis in the age of precision medicine. *Allergo J Int* **34**, 57–68 (2025)	
	British Society for Immunology Clinical Immunology Professional Network	Suggested reworking of Background: Mast cells release large amounts of histamine and other mediators into the blood, causing symptoms such as skin rash, itchy skin, hot flushes, blood pressure changes, fainting, tachycardia, headache, vomiting, diarrhoea, brain fog, organ failure and anaphylaxis. In indolent mastocytosis, mast cells are able to release their contents and cause these symptoms without specific trigger resulting in intermittent but recurrent and often severe symptoms.	We have updated the background section.
Population	Blueprint Medicines (company)	Population definition should be aligned with anticipated marketing authorisation and PIONEER trial participants.[21,34] The suggested amendment (below) to the following wording would reflect the target population more accurately: ‘[redacted].’	We have updated the population to refer to inadequately controlled moderate to severe indolent systemic mastocytosis.
	British Association of Dermatologists	Yes [the population is defined appropriately]	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Allergy and Clinical Immunology	Yes [the population is defined appropriately] – patients with ISM defined by WHO criteria	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care	Yes [the population is defined appropriately]	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	Yes [the population is defined appropriately]	Thank you for your comment. No action needed.
Subgroups	Blueprint Medicines (company)	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. In the PIONEER trial (NCT03731260)[21], the randomised avapritinib vs placebo comparison at 6 months was analysed, in addition to intention-to-treat (ITT) and per-protocol (PP) populations, according to the following subgroups:[38] • Age • Gender • Region and country	Thank you for your comments. Where relevant and appropriate, subgroups may be considered by the committee if evidence allows.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Baseline ISM status • Baseline serum tryptase level • ECOG performance status • Prior TKI therapy. This analysis showed that avapritinib led to greater ISM-SAF TSS reduction than placebo across most subgroups, except in men and patients with baseline serum tryptase <20 ng/mL. These two subgroups had small sample sizes and confidence intervals crossed zero, suggesting variability in response. Even with uncertainty, many patients in these subgroups still appeared to benefit from avapritinib treatment.[38]	
	British Association of Dermatologists	The severity of skin involvement and associated symptoms may not be proportional to the overall systemic mast cell burden, as evidenced by blood tryptase levels and variant allele fraction of mutated KIT. In other words, some adults may have extensive skin involvement with low blood tryptase but other patients with a high systemic mast cell burden may have relatively few skin lesions. Given this heterogeneity, the subgroups considered should be based on symptom burden rather than systemic mast cell load alone.	Thank you for your comments. Where relevant and appropriate, subgroups may be considered by the committee if evidence allows.
	The UK Mastocytosis Support Group and Leukaemia Care	No. [there are no groups within the population that should be considered separately] The “best supportive care” is similar for everyone with moderate to severe SM and the trials have included patients along this full spectrum so data is representative for all of those patients.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology	No [there are no groups within the population that should be considered separately]	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Professional Network		
Comparators	Blueprint Medicines (company)	Blueprint Medicines considers the comparator (BSC) listed to be relevant for this submission as this reflects current NHS practice for the treatment of ISM. For this draft scope, Blueprint Medicines has provided specific detail regarding BSC in NHS clinical practice as per clinical expert structured elicitation activities.[4] According to current NHS guidance and UK clinical experts, BSC consists of antihistamines (H1/H2-blockers), proton-pump inhibitor (e.g. omeprazole), leukotriene inhibitors (e.g. montelukast), corticosteroids (e.g. prednisolone), mast cell stabilisers (e.g. sodium cromoglicate/cromolyn sodium), and monoclonal antibodies (such as omalizumab in ~5% of ISM patients).[4,5,32,33] Additionally, off-label treatments not indicated for ISM may be used such as midostaurin, imatinib, nilotinib (or dasatinib) and cladribine if the clinician believes the benefit outweighs the risk to the patient.[4,31] Notably, the NHS clinical practice aligns with European and US clinical guidance for management of ISM, with similar implementation of this tailored patient-specific BSC regimen as well as off-label therapies.[5-7,17] Notably, avapritinib for moderate-to-severe symptoms of ISM is approved by the EMA[16] and for ISM by the FDA (symptomatic patients)[39], with corresponding avapritinib references in the aforementioned clinical guidance. As per the PIONEER clinical trial, Blueprint Medicines anticipates that avapritinib will be used to address the underlying pathophysiology of ISM, alongside BSC symptom-focused therapies.[21] While this may result in reduction of BSC usage (dose/frequency) avapritinib is not planned to replace BSC.	Thank you for your comments. The specific detail of what constitutes best supportive care in NHS practice will be considered during the appraisal process. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Association of Dermatologists	[Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?] No, as there is no direct comparator to avapritinib. This is a novel technology that selectively reduces mast cell burden with associated symptoms rather limited to symptom control with anti-mast cell mediator therapies and phototherapy	Thank you for your comments. When there is no direct comparator, it is appropriate to list it as best supportive care. No action needed.
	British Society for Allergy and Clinical Immunology	"Best supportive care" includes a large range of mediations which aim to relieve symptoms but there is no currently available comparator for patients who fail to respond to BSC.	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care	Best supportive care BSC is the appropriate comparator. There are no medications approved for ISM in the UK, so all medications are used off-label. Patients with moderate to severe ISM are typically started, stepwise, on therapies meant to block the action of mast cell mediators or stabilise the mast cell so those mediators are less likely to be released. The doses of these medications may exceed the typical doses for people with, e.g. allergic conditions, for example, patients may take up to 4x the normal dose of an H1 blocker (akin to the guidelines for some forms of urticaria). This is consistent with advice from the European Competence Network on Mastocytosis (ECNM) and American Initiative on Mastocytosis (AIM) consensus guidance on treatment (Valent P, Hartmann K, Schwaab J, 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). In a survey of patients in Europe (including the UK) the mean number of medications being taken for ISM was 6. (Triggiani M, Hobart J, Alvarez-Twose I, Patient-Reported Outcomes and Provider Perceptions of	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Systemic Mastocytosis: Results from the PRISM Study. Clin Exp Allergy. 2025 Jun 27.) BSC typically includes: <u>Supportive Self-Management</u> Doctors and patients work together to identify what might trigger symptoms and strategies to avoid the triggers. This process can take considerable clinical input. The most common triggers in a patient study were: Medications, emotional stress, temperature changes, airborne chemicals, foods, alcohol and latex. (Triggiani et al). Insect venom and anaesthetics are also common triggers. <u>Anti-mediator therapy:</u> -**H1 blockers** (sometimes one H1 blocker is sufficient, and sometimes several types including 1st, 2nd and 3rd generation antihistamines) -**H2 blockers** (not only to manage hyperacidity that can occur due to high levels of histamine but also to stabilise blood pressure, manage nausea and itching. We hear from patient feedback that H2s can help with all of these.) -**Proton-pump inhibitors** (in patients where hyperacidity is not managed with an H2 blocker a PPI is often added, including in the higher of the two doses available) -**Anti-leukotriene medications** (currently only montelukast is available in the UK. It is commonly used to manage overall sensitivity to allergens and other triggers as well as to help manage respiratory symptoms or asthma if present.)	

Section	Consultee/ Commentator	Comments [sic]	Action
		-**Ketotifen** is an H1 blocker that is thought to have some mast cell stabilising properties. When it is available in the UK (supply is variable) it is often added to BSC in patients who are not well-controlled with the above medications. -**Sodium cromoglycate** (SC) is a mast cell stabiliser that is often most effective for managing cramping and diarrhoea, because its large molecule is not very well absorbed and is most effective locally (where absorbed). Many patients with moderate to severe ISM take both ketotifen and SC. -**Oral corticosteroids** (OCs) (used most commonly episodically when a patient's symptoms are not controllable—often that's repeated anaphylaxis, but sometimes other symptoms such as diarrhoea). Appropriately, their use is limited because of concerns about side effects including additional negative effects on bone on top of mastocytosis-induced osteopenia/porosis, adrenal consequences etc. We have members of our community who now live with the permanent effects of long-term use of OCs. -**Adrenaline auto-injectors** (since about half of adults with ISM will experience anaphylaxis over a lifetime, AIs should be prescribed for all patients. <u>Osteoporosis prevention:</u> Patients receiving BSC will also take **calcium and vitamin D** (usually prescribed) for prevention of osteoporosis. Some will also require treatment with **bisphosphonates or a RANK ligand inhibitor**, often starting well before the typical post-menopausal user and carrying on indefinitely. <u>Anaphylaxis prevention:</u> Occasionally patients will be given **omalizumab** if they have refractory anaphylaxis. Some patients find it helpful and others don't, which is reflected	

Section	Consultee/ Commentator	Comments [sic]	Action
		in the research literature, but we do not yet have a mechanism for identifying who will benefit. Temporary Management of Skin Symptoms **Dermovate cream under occlusion** is used for short periods to decrease skin spots and therefore itching. The benefits are temporary. **Phototherapy** such as PUVA is used to temporarily decrease skin symptoms. There is some recent evidence of an increase in the risk of melanoma in SM patients, raising additional concerns about its use, particularly given that the effects are short-lived. In our community a patient has had anaphylaxis immediately following phototherapy, likely due to the heat effects of the treatment. Immunotherapy Given the increased risk of severe anaphylaxis, people with ISM and anaphylaxis to bees and wasps should be offered **venom immunotherapy** for a lifetime. (Bonadonna P, Zanotti R, Pagani M, et al. Anaphylactic Reactions After Discontinuation of Hymenoptera Venom Immunotherapy: A Clonal Mast Cell Disorder Should Be Suspected. J Allergy Clin Immunol Pract. 2018 Jul-Aug;6(4):1368-1372)	
	British Society for Immunology Clinical Immunology	Antihistamines, sodium cromoglicate and oral corticosteroids are mentioned – could also include other supportive treatments such as H2 receptor antagonists, leukotriene inhibitors. Adrenalin for severe anaphylaxis symptoms should be included. +/- specialist haematological medications such	We have updated the treatment options in the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
	Professional Network	as other tyrosine kinases and interferon alpha although these are more for advanced systemic symptoms.	
Outcomes	Blueprint Medicines (company)	Blueprint Medicines agrees that the outcomes listed in the draft scope are appropriate and generally aligned with those assessed in the key trials, except for mortality. The key outcomes (as per the disease pathogenesis and the PIONEER trial) are symptom severity/burden (and reduction thereof), objective measures of mast cell burden, HRQoL, and safety profile.[20,38] Notably, mortality is captured only as an adverse event (AE).[20] In patients with ISM, observational cohort evidence shows that overall survival (OS) remains poorer compared to the general population and in individuals with cutaneous mastocytosis (non-SM).[15,40,41] Considering these published mortality studies, the PIONEER clinical trial follow-up is relatively short (only ~3 years) thus survival data is immature for robust analysis.[21] With this in mind, Blueprint Medicines suggests positioning mortality at the lower end of the outcomes hierarchy to reflect its limited relevance in ISM relative to symptom burden and HRQoL. As such mortality is included this submission only in the context of economic modelling for cost-effectiveness and clinical safety profile.	Thank you for your comments. The order of outcomes does not reflect their importance. The committee will discuss all relevant outcomes, including input from relevant stakeholders on the outcomes most important to people with indolent systemic mastocytosis. No action needed.
	British Association of Dermatologists	Yes [outcomes listed are appropriate]	Thank you for your comments. No action needed.
	British Society for Allergy and Clinical Immunology	The outcome seem sensible.	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	The UK Mastocytosis Support Group and Leukaemia Care	All of the outcomes listed are appropriate and will capture the most important health related benefits of the technology that can most easily be quantified. Both of the following outcomes are challenging to quantify and we recognise that they will be difficult to measure in QALYs, but want to acknowledge that this is a limitation of the process. <u>Employment</u> We may find that we have some data to offer that would allow some measurement of the benefit of continued employment on the psychological health of the patient. We will endeavour to capture this with published and additional data and stories from our patient community the effect on employment. Given that ISM predominantly effects people of working age, the effects of ISM on people's ability to hold a job is of significance when costs to society are looked at holistically. The recent PRISM study of patients and provider experiences with systemic mastocytosis (Triggiani et all, 2025—see the additional data in online repository) found that half of the ISM UK patients who responded to the survey question (n=50) had decreased their working. (This study included patients of any severity.) Sixteen percent had voluntarily quit their jobs because of their ISM and 6% had been terminated. Eighteen percent had left work and received disability payments and 8% had taken early retirement. Forty-seven percent of UK healthcare providers surveyed (n=110) about the effects of ISM on ability work said that it affected ability to work a great deal or quite a bit, 38% said it affected patients somewhat, with only 1% saying it had no effect.	Thank you for your comments. NICE takes an NHS and personal and social services perspective when assessing cost effectiveness. The evaluation will consider health effects for carers when relevant. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers. The appraisal committee will consider if there is evidence that introducing the technology may lead to identifiable benefits that are not captured in the

Section	Consultee/ Commentator	Comments [sic]	Action
		Effect on Carers Moderate to severe ISM can also have effects on carers, including on their own ability to hold full-time employment and manage childcare obligations. We will share carer stories in the next phase of the evaluation. Psychological Effects Living with a chronic and episodic, unpredictable, life-threatening condition can be extremely challenging. We also note that it is difficult to quantify the psychological effects on patients of living with ISM. This is in part because it can be difficult for doctors to elicit an accurate picture of what patients experience from day to day, in part because patients may want to look stoical and not complain. We will endeavour to communicate that with our later submission of evidence. ISM adds an additional layer of misery because "trigger-avoidance" is a key strategy for minimising mast cell activation (and thereby minimising symptoms) but that avoidance often involves making significant lifestyle changes that dramatically reduce patient quality of life.	cost effectiveness analysis.
	British Society for Immunology Clinical Immunology Professional Network	Symptom severity and health related quality of life more important than mortality as 99% of individuals have normal lifespan	Thank you for your comments. NICE keeps the outcomes list inclusive. The most appropriate outcomes will be discussed by the committee. The order of outcomes does not reflect their importance.

Section	Consultee/ Commentator	Comments [sic]	Action
			The committee will discuss all relevant outcomes, including input from relevant stakeholders on the outcomes most important to people with indolent systemic mastocytosis.
Equality	Blueprint Medicines (company)	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.[42]	Thank you for your comments. The EIA has been updated to address this point.
	British Association of Dermatologists	[are there any equalities issues that mean the draft scope or remit need changing?] None that we can identify.	Thank you for your comment. No action needed.
	British Society for Allergy and Clinical Immunology	I don’t foresee any issues.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	The UK Mastocytosis Support Group and Leukaemia Care	No specific concerns. We do have a concern that patients across the UK should have equal access to avapritinib when it is approved and not just those who have access to a reference centre.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	No issues	Thank you for your comment. No action needed.
Questions for consultation	Blueprint Medicines (company)	**Where do you consider avapritinib will fit into the existing care pathway for indolent systemic mastocytosis?** As per previous structured expert elicitation activities with UK clinical experts and the PIONEER trial (NCT03731260 [redacted] .[4,20] Since BSC therapy would not stop, avapritinib would be used as [redacted].[4] **How are symptoms of indolent systemic mastocytosis measured in clinical practice? How would moderate and severe symptoms be defined?** For NHS clinical practice, there is a lack of information on the treatment response criteria specifically for ISM.[4] Contrary to PIONEER phase 2 clinical study, clinical efficacy in NHS clinical practice (response to treatment) is routinely evaluated according to clinician judgement, not via patient-reported	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		outcome (PRO) measures.[4] Currently, no PRO tools (such as ISM-SAF) have been adopted or are widely used in day-to-day clinical practice. Moderate-to-severe disease is designated based on clinician assessment.[4] As part of the PIONEER trial, clinician assessment was used in tandem with ISM-SAF for patients with a WHO-defined diagnosis of ISM.[20,21,38] Diagnosis of ISM in clinic and the PIONEER trial is based on set WHO criteria recommended by clinical guidelines.[5,7,15,17,43] From clinical expert engagement, response to treatment and ISM severity is primarily gauged in terms of most severe symptom(s), quality of life burden, and impact on activities of daily life.[4] **Please select from the following, will avapritinib be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** As with other SM conditions, such as AdvSM, avapritinib is expected to be prescribed in secondary care (within NHS centres of excellence and specialist clinics) with routine follow-up in secondary care based on a multidisciplinary team (MDT) approach. Blueprint Medicines advise that follow-up setting is dependent on severity of the patient, but those with moderate-to-severe symptoms will be monitored in secondary care as standard practice. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**	

Section	Consultee/ Commentator	Comments [sic]	Action
		For avapritinib treatment of patients with ISM, the treatment setting is anticipated to be the same as for BSC. From clinical data arising from PIONEER study, Blueprint expect BSC usage (dose/frequency) will decrease as a result of avapritinib's clinical efficacy (i.e. reduction of symptom burden).[4,44] No indication that routine follow-up would be different for avapritinib compared to BSC.[4] **Would avapritinib be a candidate for managed access?** Blueprint Medicines does not believe that avapritinib would be suitable for managed access. While the open-label phase of the PIONEER trial is ongoing[21], there are no further clinical development plans for this indication, and there are expected to be limited additional evidence that would reduce any uncertainties in the clinical- or cost-effectiveness case. **Do you consider that the use of avapritinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Most of the primary and secondary outcomes pf the PIONEER trial have been incorporated into the calculation of quality-adjusted life years (QALY) values. This includes symptom burden, mast cell burden, HRQoL, and safety outcomes which are improved with avapritinib (plus BSC) equating to an improved health state. Aside from these key outcomes, other data from PIONEER participants was reported, which while important, was not utilised in the economic modelling. For instance, the cost of BSC therapies is included in the economic modelling, but the effect of avapritinib on the specific usage of BSC (i.e. dose and frequency) is not. Notably, avapritinib plus BSC has demonstrated a 21% reduction in BSC usage versus a 13% reduction in patients treated with	

Section	Consultee/ Commentator	Comments [sic]	Action
		placebo plus BSC.[44] This reduction in polypharmacy and treatment burden is relevant to this disease with its wide range of symptoms and associated burden. Despite the heterogeneity of ISM, anaphylaxis is commonly reported in patients with ISM (frequency ranging from 20% to 49%), and episodes have the potential to be life-threatening necessitating epinephrine auto-injectors availability at all times.[45] Within the PIONEER trial, anaphylactic episodes, based on epinephrine usage, were included as an exploratory endpoint. Of patients who received avapritinib (25 mg) with baseline anaphylaxis (N=8), six of these patients had no events in the randomised Part 2 of the PIONEER study. Overall, avapritinib-treated patients had fewer anaphylaxis episodes compared to those who had received placebo over a 6-month period. Notably, the short study duration and limited number of reported cases make interpretation difficult and only partially reflects the true burden of anaphylaxis.[45] Impaired bone health routinely presents as musculoskeletal complications (including osteoporosis, osteopenia, and fragility fractures) in patients with ISM.[46,47] This was reflected by the PIONEER trial which reported 48 (19%) patients with osteopenia and 56 (22%) patient with osteoporosis.[48] Following two years of avapritinib treatment (plus BSC), patients (n=13-14) demonstrated an increase in bone mineral density (BMD) ranging from 2.21% to 4.79% depending on the measurement site. These magnitudes of BMD 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.[48] From 3 years of follow-up in the PIONEER OLE phase, avapritinib is shown to be an effective therapeutic option for patients with ISM due to its	

Section	Consultee/ Commentator	Comments [sic]	Action
		favourable, long-term benefit-risk profile.[35] In terms of long-term efficacy and safety of avapritinib (incorporated into the economic modelling of ISM), the PIONEER trial (NCT03731260)[21] demonstrates sustained disease control and reduction in disease burden markers with avapritinib (plus BSC) alluding to a disease-modifying effect that could plausibly reduce the risk of progression to more advanced forms of disease (such as AdvSM).[35,49] **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The primary data source for demonstrating clinical efficacy and safety is the PIONEER Phase 2 study (NCT03731260) with a 3-part study design including randomised part evaluating avapritinib vs placebo at 24 weeks and an OLE phase (up to 3 years).[20,21] The multinational, PRISM patient survey was undertaken to facilitate understanding of the experiences of patients with SM (including ISM).[25,29] This multinational, comprehensive study assessed symptoms (ISM-SAF), QoL (SF-12), global health assessment (EQ-5D), and work/activity impairment (WPAI).[50] Elements of the PRISM were utilised to inform the economic model and the description of disease burden in this dossier. **Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.**	

Section	Consultee/ Commentator	Comments [sic]	Action
		In addition to BSC, other TKIs such as midostaurin, imatinib, and dasatinib may be administered to patients with ISM despite their off-label status. This aligns with current EU and NCCN clinical guidance, as well as available NHS information on mastocytosis.[5,7,51] Contrary to these suboptimal TKI options, avapritinib represents a step-change in ISM management by high affinity targeting of *KIT D816V* mutation in mast cells.[16,36] Avapritinib is not approved for use in NHS clinical practice for ISM, aside from the ongoing PIONEER clinical trial.[21] If recommended by NICE, avapritinib will be used in line with its marketing authorisation for 25 mg dosage per day in patients with moderate-to-severe ISM inadequately controlled on BSC.[16,34,39] This aligns with the pivotal PIONEER phase 2 trial in which avapritinib was administered daily (25 mg) plus BSC.[21] It should be noted that a proportion of patients with greater disease burden at baseline required dose escalation (upon entry into an open-label phase rather discontinuing the study), to a 50 mg dose.[35] This has been accounted for in this submission's economic modelling and clinical effectiveness findings.	
	British Association of Dermatologists	**Where do you consider avapritinib will fit into the existing care pathway for indolent systemic mastocytosis?** Patients with active symptoms not controlled with conventional treatment. It would be helpful to include all patients with moderate or severe symptoms irrespective of their tryptase levels. **What treatments are included in best supportive care for indolent systemic mastocytosis?** 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 occasional off-label use of omalizumab for uncontrolled anaphylaxis	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		Is avapritinib expected to be used instead of or in addition to currently available treatments? In addition to currently available treatments. **How are symptoms of indolent systemic mastocytosis measured in clinical practice?** Patient evaluation of itch, rash, skin flushing, GI symptoms, headaches, brain fog, and urinary symptoms can be measured with QoL scores including the Dermatology Life Quality Index (DLQI). Other PROMS that can be used to assess symptom activity include the disease-specific Mastocytosis Quality of Life (MC-QoL) and Short Form Health Survey (SF-12). Total symptom scores may be used, such as the ISM-SAF score reported in the reported phase 2 trial of avapritinib (NEJM Evid 2023; 2 (6) Episodes of anaphylaxis recorded. Objective testing for disease severity and progression includes regular blood monitoring for blood count, liver profile, tryptase levels, blood KIT Variant Allele Fraction (when available) and DEXA scans. **How would moderate and severe symptoms be defined?** Total symptom score of ≥ 28 using the ISM symptom assessment form (ISM-SAF) described in the phase 2 study of avapritinib. The Dermatology Life Quality Index of >10 could be used as a simple clinic screening PROM for patients presenting to dermatologists who might be suitable for further assessment with the ISM-SAF. **Please select from the following, will avapritinib be:** ~~A. Prescribed in primary care with routine follow-up in primary care~~	

Section	Consultee/ Commentator	Comments [sic]	Action
		~~B. Prescribed in secondary care with routine follow-up in primary care~~ C. Prescribed in secondary care with routine follow-up in secondary care ~~D. Other (please give details)~~ **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** N/A. **Would avapritinib be a candidate for managed access?** Yes. **Do you consider that the use of avapritinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** If the EQ-5D is used as the primary tool for assessing the QALY calculation, it would not take account of the highly deleterious impact that the appearance of cutaneous lesions of mastocytosis (syn. urticaria pigmentosa) may have on the self-confidence and lifestyle opportunities for patients with extensive skin involvement.	
	British Society for Allergy and Clinical Immunology	I see avapritinib as being an additional treatment for patients with ISM who have persistent symptoms despite an optimised regimen of BSC. There is currently no additional treatment that can be offered to these very symptomatic patients unless they progress to advanced SM. BSC includes H1 and H2 antihistamines, leukotriene antagonists, sodium cromoglycate (Nalcrom), proton pump inhibitors, occasionally omalizumab, topical corticosteroids, topical calcineurin inhibitors, UV therapy, loperamide/anti-diarrhoeal medicines.	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		Importantly some of these like Nalcrom, ketotifen, and omalizumab, are used off-licence; UV was previously a widely-used treatment but is no longer popular due to the increased risk of skin cancers. Avapritinib would be an additional treatment to these, although its use may result in changes to doses/medications depending on how the avapritinib helps/affects the symptom profile. Symptoms of ISM are measured with physician global assessment, and patient description of individual symptoms and their worst symptoms. There is no universal symptom scoring system although some are available and may be used in different centres. Avapritinib would be prescribed and followed-up in secondary care only It would be suitable for managed access although I think there is sufficient evidence to make a recommendation.	
	The UK Mastocytosis Support Group and Leukaemia Care	*Where do you consider avapritinib will fit into the existing care pathway for indolent systemic mastocytosis?* Our expectation is that avapritinib will be used in patients who are not getting good control of symptoms from BSC. We expect that consultants will initiate anti-mediator therapy as outlined above under Comparators, using the therapies that are appropriate for the patient's particular symptoms. Because of the nature of ISM, with its diverse presentation and often hypersensitive patients, patients may not tolerate (or benefit from) all of the medications listed as possible BSC and these lists should not be considered as a necessary checklist before avapritinib would be considered. The consensus guidelines from the ECNM and AIM are a reasonable description of how that stepwise treatment might be tried, and the team who developed them included UK doctors. (Valent et al, 2022) *What treatments are included in best supportive care for indolent systemic mastocytosis?*	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		See above under Comparators. *Is avapritinib expected to be used instead of or in addition to currently available treatments?* In our observations of how avapritinib is being used in other countries we see that some patients are able to decrease the number of treatments they are using from the list of BSC, but we do not expect all patients to be able to drop all BSC. This real world experience is consistent with what was found in the trial. We would expect a decrease in the number of visits required to manage exacerbations of symptoms, including A&E and visits to mastocytosis consultants. *How are symptoms of indolent systemic mastocytosis measured in clinical practice? How would moderate and severe symptoms be defined?* This is an important question. Some clinics use tools to assess the symptoms and quality of life of their patients, but there is no single tool that is available in the public domain that has been adopted in the UK or in any other country for this purpose. In our view the ISM-SAF, used in the trial, is measuring the appropriate domains. Patients usually will have symptoms in more than one domain such that even if their biggest uncontrolled problem is in one area (e.g. multiple episodes of cramping and (explosive and unpredictable) diarrhoea every day) they will likely also have fatigue that is a serious issue and would thereby qualify. We do think there is room for clinical judgement and that inexperience with measuring tools might slow introduction of the drug outside of the most experienced centres. A 2023 study of 76 patients with ISM attending a UK centre of excellence found that 36% of them would be considered moderate to severe by using the	

Section	Consultee/ Commentator	Comments [sic]	Action
		ISM-SAF. (Scott Veitch, Susan Asirvatham, Priya Sriskandarajah, et al. 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, Blood, Volume 142, Supplement 1, 2023, Page 4579.) *Please select from the following, will avapritinib be:* *A. Prescribed in primary care with routine follow-up in primary care* *B. Prescribed in secondary care with routine follow-up in primary care* *C. Prescribed in secondary care with routine follow-up in secondary care* *D. Other (please give details):* *For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.* As with the current treatments, we would expect avapritinib to be prescribed and routinely followed up in secondary care. Treatment with BSC is currently generally initiated in secondary care (unless a patient has been given some anti-mediator therapy by a sharp-eyed GP who has then referred them to a consultant for diagnosis) and GPs then continue the prescriptions as guided by the consultant. At present ISM patients would be seen at least annually by the consultant and those with moderate to severe symptoms are usually seen twice a year for monitoring and assessment of symptoms and tweaking of BSC medications, and more frequently if there is a flare of symptoms, significant change in well-being, or concern about possible progression. Because of the risk of progression from indolent to more advanced forms of SM, ISM patients ought never to be discharged from secondary care. *Would avapritinib be a candidate for managed access?*	

Section	Consultee/ Commentator	Comments [sic]	Action
		We understand that there is sufficient compelling data available to show safety and efficacy, including a body of real-world evidence from its use in Europe and the US. *Do you consider that the use of avapritinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* See discussion above about employment, carers and psychological concerns and the data available. *Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.* Doses for anti-mediator therapies are often higher than those listed in the BNF. In particular, H1 blockers are often used in higher doses than they would be for allergies consistent with use in other conditions where histamine levels are high such as some types of urticaria. None of the anti-mediator therapies are specifically approved for ISM.	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	British Association of Dermatology	Any additional comments on the draft scope Avapritinib is the first, highly selective tyrosine kinase inhibitor (TKi) to be trialled for improving the lives of adult patients with indolent systemic mastocytosis who may be managed by dermatologists or haematologists. The clinical trials indicate that it is safe and effective as an add-on treatment to best supportive care. It is already li.censed for patients with advanced sytemic mastocytosis who are cared for by haematologists. Extension of its use to moderately to severely affected adult patients with ISM not responding to best supportive care would represent a step change in the management of options for this small but important cohort of patients.	Thank you for your comments. No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

n/a

References:

1. Azaña J. M., Torrelo A., Matito A. Actualización en mastocitosis. Parte 2: categorías, pronóstico y tratamiento. *Actas Dermo-Sifiliográficas.* 2016;107(1):15–22.
2. Livideanu C. Mastocytoses non-avancées chez l'adulte. Centre des Référence des Mastocytoses (CEREMAST) et Filière de Santé Maladies Rares Immuno-Hématologique (MaRIH). 2022. 2022; https://www.has-sante.fr/upload/docs/application/pdf/2022-07/pnds_mastocytoses_non_avancees.pdf. Accessed 14 December, 2022.
3. Schwaab J., Balabanov S., von Bubnoff N., et al. Maystozytose, systemische. 2024; https://www.onkopedia.com/de/onkopedia/guidelines/mastozytose-systemische/@@guideline/html/index.html#ID0EWSAG. Accessed 11 March, 2024.
4. *Blueprint Medicines Corporation: [Data on file] Clinical expert (KOL) validation summary report.* 2025.
5. Valent P., Hartmann K., Bonadonna P., et al. European Competence Network on Mastocytosis (ECNM): 20-Year Jubilee, Updates, and Future Perspectives. *J Allergy Clin Immunol Pract.* 2023;11(6):1706–1717.

6. Valent P, Hartmann K, Schwaab J, et al. Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice. *The Journal of Allergy and Clinical Immunology: In Practice.* 2022;10(8):1999–2012.e1996.
7. Gotlib J., Gerds A. T., Abdelmessieh P., et al. NCCN Guidelines(R) Insights: Systemic Mastocytosis, Version 3.2024. *J Natl Compr Canc Netw.* 2024;22(2 D).
8. Theoharides TC., Valent P., Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med.* 2015;373(2):163–172.
9. Magliacane D., Parente R., Triggiani M. Current concepts on diagnosis and treatment of mastocytosis. *Transl Med UniSa.* 2014;8:65–74.
10. Matito A., Morgado JM., Alvarez-Twose I., et al. Serum tryptase monitoring in indolent systemic mastocytosis: association with disease features and patient outcome. *PLoS One.* 2013;8(10):e76116.
11. Mayado A., Teodosio C., Garcia-Montero A. C., et al. Increased IL6 plasma levels in indolent systemic mastocytosis patients are associated with high risk of disease progression. *Leukemia.* 2016;30(1):124–130.
12. Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, et al. Frequency and prognostic impact of KIT and other genetic variants in indolent systemic mastocytosis. *Blood.* 2019;134(5):456–468.
13. Mukherjee S., Pemmaraju N., Shaheen D., Green T. Disease Worsening and Progression in Patients with Indolent Systemic Mastocytosis: A US Population-Level Analysis Using Health Claims-Based Dataset. AAAAI Annual Meeting 2023; 24–27 February, 2023; San Antonio, TX.
14. NICE. TA1012: Avapritinib for treating advanced systemic mastocytosis. 2024; https://www.nice.org.uk/guidance/ta1012. Accessed 05/02/2025, 2025.
15. Trizuljak J., Sperr W. R., Nekvindova L., et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. *Allergy.* 2020;75(8):1927–1938.
16. EMA. *European Medicines Agency. Avapritinib. Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.* 2025.
17. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. *Am J Hematol.* 2023;98(7):1097–1116.
18. Garcia-Montero AC., Jara-Acevedo M., Teodosio C., et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood.* 2006;108(7):2366–2372.
19. George T. , Hoehn G., Lin H-M., Miller S., Akin C. Increased detection of KIT D816V mutation in peripheral blood samples from patients with indolent systemic mastocytosis (ISM) in the phase 2 pioneer study using a high sensitivity droplet digital (dd) PCR assay compared with next generation sequencing (NGS). *Blood.* 2020;136:7–8.
20. Gotlib J., Castells M., Elberink H. O., et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. *NEJM Evid.* 2023;2(6):EVIDoa2200339.

21. NCT03731260: A 3-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate Safety and Efficacy of Avapritinib (BLU-285), a Selective KIT Mutation-Targeted Tyrosine Kinase Inhibitor, in Indolent and Smoldering Systemic Mastocytosis With Symptoms Inadequately Controlled With Standard Therapy. 2018. https://clinicaltrials.gov/study/NCT03731260.
22. Pulfer S., Ziehfreund S., Gebhard J., et al. Health-Related Quality of Life and Influencing Factors in Adults with Nonadvanced Mastocytosis - A Cross-Sectional Study and Qualitative Approach. *J Allergy Clin Immunol.* 2021;9(8):3166–3175.e3162.
23. Mesa R , Sullivan E., Dubinski D., et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient S urvey. *Cancer.* 2022;128(20):3691–3699.
24. Jennings S. V., Slee V. M., Zack R. M., et al. Patient Perceptions in Mast Cell Disorders. *Immunology and allergy clinics of North America.* 2018;38(3):505–525.
25. Mesa R., Triggiani M., Hobart J., et al. PCR136 The Burden of Systemic Mastocytosis in Select European Countries: Evidence from the Prism Patient Survey. *Value in Health.* 2023;26(12):S475.
26. Triggiani M, Radia D, Livideanu C., et al. Abstract 000405: The burden of indolent systemic mastocytosis in Europe: Results from the prism patient survey. *Allergy.* 2024;79(S113):3–164.
27. Jensen B., Broesby-Olsen S., Bindslev-Jensen C., Nielsen D. S. Everyday life and mastocytosis from a patient perspective-a qualitative study. *J Clin Nurs.* 2019;28(7-8):1114–1124.
28. UK Mastocytosis Support Group. 2024; https://ukmasto.org/about-mcd/#gsc.tab=0.
29. Blueprint Medicines Corporation: *[Data on file] PRISM Perceptions, Realities, and Insights on Systemic Mastocytosis from 7 European Countries.* . 2023.
30. CEREMAST. *A study by CEREMAST of the epidemiology and management of adults with mastocytosis in France: A national survey of allergists, dermatologists, internists, hematologists, and rheumatologists.* 2023.
31. NHS. Mastocytosis: Overview, symptoms and treatment. 2024; https://www.nhs.uk/conditions/mastocytosis/.
32. Oni C., Moonim M., Desterro J., et al. UK Single Institution Experience of Mastocytosis: Guy's and St Thomas' NHS Foundation Trust. *Blood.* 2019;134:2960.
33. Veitch S., Asirvatham S., Sriskandarajah P., et al. 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. *Blood.* 2023;142(Supplement 1):4579–4579.
34. *Blueprint Medicines Corporation: [Data on file] Draft avapritinib UK SmPC (summary of product characteristics).* 2023.
35. Elberink H. O., Akin C, Castells M, et al. Favorable Benefit-Risk Profile of Avapritinib in Indolent Systemic Mastocytosis Is Maintained After 3 Years of Therapy: Longer-Term Analysis of the PIONEER Study. Paper presented at: EAACI2025.
36. Castells M. Efficacy and Safety of Avapritinib in Indolent Systemic Mastocytosis (ISM): Results from the Double Blind Placebo Controlled PIONEER Study. Paper presented at: AAAAI2023.
37. Castells M., Akin C., Maurer M., et al. Long-term Quality of Life and Safety in Patients with Indolent Systemic Mastocytosis Treated with Avapritinib in the PIONEER Study. *Journal of Allergy and Clinical Immunology.* 2025;155(2):AB171.
38. *Blueprint Medicines Corporation: [Data on file]: Avapritinib PIONEER Clinical Study Report.* 2022.

39. FDA. *U.S Food and Drug Administration. AYVAKIT® (avapritinib). Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212608s013lbl.pdf*. 2023.
40. Kibsgaard L., Deleuran M., Flohr C., Langan S., Braae Olesen A., Vestergaard C. How "benign" is cutaneous mastocytosis? A Danish registry-based matched cohort study. *Int J Womens Dermatol.* 2020;6(4):294–300.
41. Mukherjee S., Cattie DJ., Shaheen D., Powell D., Green T. Decreased Survival Among Patients with Indolent Systemic Mastocytosis: A Population-Level Retrospective Cohort Analysis Using Healthcare Claims Dataset. *Blood.* 2023;142:75.
42. UK Medicines Information. What factors to consider when advising on medicines suitable for a Halal diet? 2020; https://www.sps.nhs.uk/wp-content/uploads/2018/01/UKMi_QA_Halal_Aug20-FINAL.doc. Accessed 08 August, 2023.
43. Valent P., Sotlar K., Horny H. P., Arock M., Akin C. World Health Organization Classification and Diagnosis of Mastocytosis: Update 2023 and Future Perspectives. *Immunol Allergy Clin North Am.* 2023;43(4):627–649.
44. Akin C., Gotlib J., Alvarez-Twose I., et al. Reductions in Polypharmacy for Patients with Indolent Systemic Mastocytosis on Avapritinib. *Journal of Allergy and Clinical Immunology.* 2024;153(2).
45. Pongdee T., Yi C. Arana, Dybedal I., Newberry K., Vachhani P. Anaphylaxis in patients with indoent systemic mastocytosis (ISM): A severe, potentially life-threatening complication. *Annals of Allergy, Asthma & Immunology.* 2023;131(5, Supplement 1):S121.
46. Degboe Y., Nezzar C., Alary P., Maeva M., Bulai Livideanu C., Laroche M. Management of Bone Health in Adult Mastocytosis. *Curr Osteoporos Rep.* 2025;23(1):10.
47. van der Veer E., van der Goot W., de Monchy J. G., Kluin-Nelemans H. C., van Doormaal J. J. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. *Allergy.* 2012;67(3):431–438.
48. Siebenhaar Frank, Alvarez-Twose Ivan, Sundaresh Vishnu, et al. Avapritinib and Bone Health in Indolent Systemic Mastocytosis: Learnings from the PIONEER Trial. *Journal of Allergy and Clinical Immunology.* 2025;155(2):AB168.
49. Veitch S., Radia D. H. Recent Advances in the Therapeutic Management of Advanced Systemic Mastocytosis. *Diagnostics (Basel).* 2023;14(1).
50. 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.
51. Valent P., Hartmann K., Hoermann G., et al. Harmonization of Diagnostic Criteria in Mastocytosis for Use in Clinical Practice: WHO vs ICC vs AIM/ECNM. *J Allergy Clin Immunol Pract.* 2024;12(12):3250–3260 e3255.