National Institute for Health and Care Excellence

Single Technology Appraisal
Avapritinib for treating advanced systemic mastocytosis [ID3770]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Blueprint Medicines (UK) Ltd	Blueprint Medicines believes that the evaluation of avapritinib, by NICE, for the treatment of advanced systemic mastocytosis (AdvSM) is appropriate due to the high unmet medical need and lack of efficacious, targeted treatments for people living with AdvSM, as is outlined below. Blueprint Medicines believes that a cost comparison evaluation is the appropriate route to establish the clinical and cost effectiveness of avapritinib for the treatment of AdvSM, since avapritinib meets all the requirements for the cost comparison route (as described in the section 'Questions for consultation' below).	Thank you for your comment. No action needed
	British Society for Haematology	YES STA technology route seems appropriate or cost comparison if feasible.	Thank you for your comment. No action needed
	The UK Mastocytosis Support Group and Leukaemia	We view this evaluation as entirely appropriate because avapritinib has shown better efficacy than existing drugs both in trials and in the real world of normal clinic use in the UK in a compassionate use setting. Patients with a rare, life-shortening haematologic neoplasm should have access to a medication that has improved outcomes over existing treatments including	Thank you for your comment. No action needed

Section	Stakeholder	Comments [sic]	Action
	Care (joint submission)	increased life expectancy and improved quality of life (Reiter A et al Leukemia. 2022; 36:2108-2020. Pilkington H, Et al Future Oncol. 2022 Apr;18(13):1583-1594.). It appears also to expand access for some patients to curative bone marrow transplant (based on discussions with UK haematologists). Advanced systemic mastocytosis causes severely shortened life expectancy. The largest (n=259) study to date of life expectancy in advanced mastocytosis found median overall survival of 5.7 years (95% CI 0.6–4.5) for patients with aggressive systemic mastocytosis, 1.9 years (0.0–5.2) for those with mast cell leukaemia, and 2.9 years (2.5–3.3) for individuals with systemic mastocytosis with an associated haematological neoplasm. (Sperr WR et al. Lancet Haematol. 2019 Dec;6(12):e638-e649.) We cannot comment as to the appropriateness of the cost comparison route vs. single technology appraisal, because neither charity has experience with the cost comparison route.	
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed
Wording	Blueprint Medicines (UK) Ltd	Blueprint Medicines would like to clarify that the remit and evaluation objective is to appraise the clinical- and cost-effectiveness of avapritinib within its marketing authorisation for treating advanced systemic mastocytosis	Thank you for your comment. The scope has been updated to reflect this.

Section	Stakeholder	Comments [sic]	Action
		(AdvSM), rather than for treating systemic mastocytosis, as is stated in the draft remit.	
	British Society for Haematology	Overall wording is generic to systemic mastocytosis (SM)and this scope needs to focus on patients with advanced systemic mastocytosis (AdvSM)	Thank you for your comment. The scope has been updated to reflect this.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	The wording of the remit leaves out a key definer of the population in question. It should read: "To appraise the clinical and cost effectiveness of avapritinib within its marketing authorisation for treating ADVANCED systemic mastocytosis."	Thank you for your comment. The scope has been updated to reflect this.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed
Timing issues	Blueprint Medicines (UK) Ltd	The timing of this appraisal is appropriate as there remains a high unmet medical need for patients with AdvSM. AdvSM is a debilitating and fatal disease that severely impacts patients' HRQoL.[1-3] Treatment protocols for AdvSM have previously focused on treating symptoms and employing off-label therapies with poor efficacy and safety profiles.[4] Patients with AdvSM still have a poor prognosis despite available	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
		therapies, such as midostaurin, a multi-kinase inhibitor (which is currently the only NICE-recommended treatment for AdvSM).[5] Median overall survival following first-line treatment with midostaurin is between 28 to 50 months, as reported in clinical and real-world studies.[6-9] Contrary to midostaurin, avapritinib is a highly selective and potent kinase inhibitor which was designed specifically to target the KIT D816V mutation, the driver of the disease in 95% of cases with systemic mastocytosis. This potency against KIT D816V has been translated into a response to therapy, complete remission and overall survival which are significantly higher compared to midostaurin, as demonstrated in an indirect treatment comparison.[10] In the indirect treatment comparison, patients who were treated with avapritinib first-line had better overall survival (adjusted hazard ratio (HR) (95% confidence interval (CI)): 0.37 (0.19, 0.73)) compared to patients treated with midostaurin.10 An analysis of patients treated with avapritinib in the EXPLORER and PATHFINDER studies compared with patients treated with best available therapy, which includes midostaurin, in an external control study, also indicated significantly improved survival with avapritinib.[11] The only established curative treatment option for patients with AdvSM is haematopoietic stem cell transplant (HSCT), however only a small proportion of AdvSM patients are eligible for, and subsequently undergo, HSCT. A treatment that improves remission rates and offers an opportunity of complete remission may increase eligibility for HSCT in AdvSM. Due to the high unmet need and the potential for avapritinib as a targeted therapy against the driver of the disease (sub-nanomolar specificity against KIT D816V) to provide significant additional benefit for patients with AdvSM, Blueprint Medicines believes that an appraisal using a cost-comparison approach would be appropriate.	

		1. Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. *Lancet Haematol.* 2019;6(12):e638-e649. 2. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood.* 2009;113(23):5727-5736. 3. Mesa RA, Sullivan EM, Dubinski D, et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. *Cancer.* 2022;128(20):3691-3699. 4. Pardanani A. Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. *Am J Hematol.* 2016;91(11):1146-1159. 5. National Institute for Health and Care Excellence. Midostaurin for treating advanced systemic mastocytosis [ID1573] - Committee Papers. 2020; https://www.nice.org.uk/guidance/ta728/documents/committee-papers. Accessed 28 June, 2023. 6. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med.* 2016;374(26):2530-2541. 7. Lübke J, Schwaab J, Naumann N, et al. Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis. *J Clin Oncol.* 2022;40(16):1783-1794. 8. Jawhar M, Schwaab J, Naumann N, et al. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. *Blood.* 2017;130(2):137-145. 9. DeAngelo DJ, George TI, Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia.* 2018;32(2):470-478. 10. Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. *Future Oncol.* 2022;18(13):1583-1594.	

Section	Stakeholder	Comments [sic]	Action
		11. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia.* 2022;36(8):2108-2120.	
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	As advanced systemic mastocytosis has shortened life expectancy and avapritinib data shows increased life expectancy it is urgent that this medication be made available as soon as possible. We know of patients whose doctors wanted to use avapritinib but the patients have died while waiting for access. While UK patients have benefitted from the approval by NICE of midostaurin, there remains considerable unmet need in advanced mastocytosis because the existing medications do not lead to a complete remission (CR) in any patients. Further, avapritinib is even more effective if it is given as first line treatment than as second line (Gotlib J et al. Nat Med. 2021 Dec;27(12):2192-2199), so more patients would benefit if it were available now rather than after they are treated with another medication such as midostaurin. Evidence from the avapritinib trials (Pathfinder and Explorer), as well as real world data from the UK from patients receiving it via compassionate use, shows that avapritinib has better outcomes than the other medications currently available in the UK in both a trial setting (Reiter A et al Leukemia. 2022; 36:2108-2020. Pilkington H, et al Future Oncol. 2022 Apr;18(13):1583-1594.) and as used in a UK clinic (Saunders et al, 2022. "The use of Avapritinib in Advanced Systemic Mastocytosis: Report of An Open-Label Compassionate Use Program in the United Kingdom", poster presented at the meeting of the American Hematology Society meeting December 2022.)	Thank you for your comment. No action needed.

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	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed
Additional comments on the draft remit	British Society for Haematology	Urgent need to have access to improved targeted therapeutic options in rare group of haematological cancer patients with life limiting disease. Avapritinib showing improved outcomes with overall survival, duration of response and quality of life compared with current available treatments.	Thank you for your comment. No action needed
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	Patients with advanced mastocytosis do not have access to curative treatments and life expectancy is still poor. In addition, patients are often highly symptomatic not only with bone pain, fatigue and symptoms related to organomegaly found in other haematologic diseases, but they also may have poorer quality of life because of their symptoms related to the release of mast cell mediators (as reported by both patients and their physicians in Mesa RA et al. Cancer. 2022 Oct;128(20):3691-3699 and Mesa RA et al. Cancer. 2022 Oct;128(20):3700-3708).	Thank you for your comment. No action needed
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Blueprint Medicines (UK) Ltd	Blueprint Medicines would like to clarify that, in addition to the symptoms listed in the background section of the draft scope, the large amounts of histamine and other mediators released by mast cells can also result in cardiac events (including changes in blood pressure, syncope and tachycardia) and neurological symptoms (including headache and brain fog).[12,13] Moreover, although the draft scope included the estimated prevalence of mastocytosis, Blueprint Medicines believes that including the estimated prevalence of systemic mastocytosis would help to narrow down the estimated number of patients with AdvSM. Orphanet has estimated the prevalence of systemic mastocytosis to be between 1:7,700 and 1:10,400 people.[14] Additionally, these estimations are closely aligned with those noted in a recent publication, which states that, based on previous publications as well as their most recent observations, the estimated prevalence of systemic mastocytosis in adults is approximately 10–13 in 100,000 residents in European countries.[15] Furthermore, the percentage of patients with systemic mastocytosis who have AdvSM is more accurately described to be 'less than 10%', compared to the 'approximately 10%' stated in the background information of the draft scope. The most recent WHO categorisation states that systemic mastocytosis includes:[16,17] • Indolent systemic mastocytosis (ISM) • AdvSM • Smouldering systemic mastocytosis (SSM) While it is estimated that approximately 90% of patients with systemic mastocytosis have ISM,[18,19] the remaining 10% will consist of patients with AdvSM or SSM.[19] Since prevalence estimations of AdvSM and SSM are not available, Blueprint Medicines believes it would be more accurate to state that less than 10% of all systemic mastocytosis patients have AdvSM.	Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
		Finally, Blueprint Medicines would like to clarify that, while treatment for AdvSM may include interferon alpha, cladribine, imatinib, nilotinib or dasatinib, none of these treatments are licensed in the UK (nor by the EMA or FDA), nor are they recommended by NICE, for the treatment of AdvSM. 12. Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. *N Engl J Med.* 2015;373(2):163-172. 13. Jennings SV, Slee VM, Zack RM, et al. Patient Perceptions in Mast Cell Disorders. *Immunol Allergy Clin North Am.* 2018;38(3):505-525. 14. Orphanet. Systemic mastocytosis. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=2467. Accessed 26 July, 2023. 15. Ungerstedt J, Ljung C, Klimkowska M, Gülen T. Clinical Outcomes of Adults with Systemic Mastocytosis: A 15-Year Multidisciplinary Experience. *Cancers (Basel).* 2022;14(16). 16. Jackson CW, Pratt CM, Rupprecht CP, Pattanaik D, Krishnaswamy G. Mastocytosis and Mast Cell Activation Disorders: Clearing the Air. *Int J Mol Sci.* 2021;22(20). 17. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405. 18. Orphanet. Indolent systemic mastocytosis. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=98848#:~:text=Disease%20definition,such%20as%20preferably%20the%20skin. Accessed 26 July, 2023. 19. UK Mastocytosis Support Group. Mastocytosis. https://ukmasto.org/about-mcd/mastocytosis/#gsc.tab=0. Accessed 26 July, 2023.	Thank you for your comment. The scope has been updated to reflect this. Midostaurin, cladribine, interferon alpha and imatinib have been kept in the scope. The technology appraisal committee will consider all evidence when deciding on appropriate comparators.
	British Society for Haematology	Mastocytosis is a condition caused by excessive amounts of neoplastic mast cells invading in body tissues, such as the skin, organs and bones. In many cases, mastocytosis is caused by a mutation in the KIT gene. Mastocytosis is	Thank you for your comment. The scope

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		generally classified as cutaneous (affecting the skin) or systemic (affecting the internal organs). The mast cells release large amounts of histamine and other mediators into the blood, causing symptoms such as skin rash, itchy skin, hot flushes, vomiting, diarrhoea, cognitive disturbances described as 'brain fog and anaphylaxis. There are various subtypes of systemic mastocytosis defined by level of mast cell disease burden and the impact. These include indolent* systemic mastocytosis that accounts for about 90% of cases of systemic disease)[1], and advanced systemic mastocytosis. In advanced systemic mastocytosis, mast cells accumulate and proliferate in internal organs and cause organ damage, bone fractures and changes in blood counts e.g. anaemia,thrombocytopenia and deranged liver function tests. The wide-ranging symptoms can be disabling and are life-threatening leading to a significantly decrease life expectancy/ survival. Advanced systemic mastocytosis includes aggressive systemic mastocytosis, systemic mastocytosis with associated haematologic neoplasm and mast cell leukaemia.[2] *Some cases of patients with high mast cell disease burden with a WHO diagnosis of indolent disease may progress so calling it non progressive in not correct. There is no cure for advanced systemic mastocytosis, treatment aims to decrease the number of mast cells and to control symptoms. Therefore, treatment depends on the symptoms experienced by each person. NICE technology appraisal 728 recommends midostaurin as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm, or mast cell leukaemia in adults. Other treatments for advanced systemic mastocytosis may include interferon alpha**, cladribine, imatinib (for disease without the KIT mutation), nilotinib*** or dasatinib.[4]	has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this.

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		** Rarely used in AdvSM post Midostaurin as ineffective *** These were tried as are tyrosine kinase inhibitors but have proven to be ineffective and so are no longer on any treatment alogrithm	
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	1. We have outlined changes we think ought to be made to the background information below by crossing out and highlighting changes/additions to the text. 2. Paragraph 1, sentence 1. ~~3.~~ Mastocytosis is a condition caused by excessive amounts of mast cells gathering in body tissues, such as the skin, ~~organs~~ GI tract, bone marrow, spleen liver, and lymph nodes. ~~and bones.~~ 4. Paragraph 1, sentence 2. 5. The mast cells release large amounts of histamine and other mediators into the blood, causing symptoms such as skin rash, itchy skin, hot flushes, vomiting, diarrhoea and anaphylaxis, as well as organ failure when they infiltrate the spleen, liver and bone marrow. 6. Paragraph 2, sentence 1. 7. There are various subtypes of systemic mastocytosis defined by level of disease ~~progression~~ involvement. These include indolent systemic mastocytosis (a highly symptomatic, but less likely to be life shortening ~~non-progressive~~ form of systemic mastocytosis that accounts for about 90% of cases of systemic disease)[1], and advanced systemic mastocytosis.	Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this.

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		8. Paragraph 2, sentence 3. 9. The wide-ranging symptoms ~~can be~~ are disabling and lead to shortened life expectancy. ~~or even life-threatening.~~ 10. Paragraph 4, sentence 2. There is no cure for advanced systemic mastocytosis. ~~treatment aims to decrease the number of mast cells and to control symptoms. Therefore, treatment depends on the symptoms experienced by each person.~~ Treatment is aimed at reducing the mast cell burden and reducing or reversing end organ damage, with the goal of extending life and reducing symptoms to improve quality of life. Other treatments for advanced systemic mastocytosis may include interferon alpha, cladribine, and imatinib (for disease without the KIT mutation)~~, nilotinib or dasatinib~~.	Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	Our experts note that the depth of information provided is limited, with much of the background being provided from (reputable) patient-directed websites rather than scientific literature directly. Our experts suggest it be expanded to give a better scientific background, especially with reference to the World Health Organization classification, which is the universal reference for the classification and which therefore	Thank you for your comment. The scope is intended to give a brief summary of the technology only. No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
		would determine the eligibility for avapritinib (as it does for midostaurin currently). A second major reference would be the National Comprehensive Cancer Network Clinical Practice Guideline (Gotlib et al, J Natl Compr Canc Netw 2018; 16:1500-1537) which provides a good background on which the studies of avapritinib built.	
Population	Blueprint Medicines (UK) Ltd	Yes, Blueprint Medicines agrees that the description of the eligible population is defined appropriately.	Thank you for your comment. No action needed.
	British Society for Haematology	Yes and needs to include all 3 sub types of patients within the category of Advanced systemic mastocytosis. Aggressive SM, Mast cell leukaemia(MCL) and SM with an associated myeloid neoplasm (SM+AMN) which make up 70% of the patients and are complex in that they have 2 co-existing haematological neoplasms.	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	Yes. The population studied in these trials, and for whom avapritinib was helpful are included in this scoping. The assessment should include the three forms of advanced systemic mastocytosis, aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematologic disorder (SM-AHN) and mast cell leukaemia (MCL).	Thank you for your comment. No action needed.
	British Society for Allergy and Clinical Immunology / Joint Committee	No comment.	No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
	on Immunology and Allergy		
Subgroups	Blueprint Medicines (UK) Ltd	Blueprint Medicines would like to clarify that this submission covers the full marketing authorisation of avapritinib for the treatment of adult patients with AdvSM. Consideration of the three disease subtypes is appropriate due to the different outcomes associated with each group. However, treatment with avapritinib in the PATHFINDER study resulted in a high response rate with deep and durable responses regardless of disease subtype.[20] The most recent analysis of PATHFINDER included 107 patients: aggressive systemic mastocytosis (ASM), n=21; systemic mastocytosis with an associated haematological neoplasm (SM-AHN), n=71; mast cell leukaemia (MCL), n=15. For the primary endpoint, the overall response rate in the overall population was 73% (95% CI 63% – 83%) compared with 77% (95% CI 46% – 95%) in the ASM subgroup, 67% (95% CI 38% – 88%) in the MCL subgroup and 75% (95% CI 61% – 85%) in the SM-AHN subgroup. Although associated with uncertainty due to small patient numbers in each group, these results indicate that the magnitude of treatment effect is similar in the three groups. In addition, generation of robust comparative evidence in the AdvSM disease subtypes will be challenging due to the small patient numbers and since baseline characteristics for each subtype are not reported in the comparator evidence (midostaurin) but will be provided if evidence allows. 20. Gotlib J, Reiter A, Radia D, Deininger M, George T. *Avapritinib in patients with advanced systemic mastocytosis (AdvSM): Efficacy and safety analyses from the phase 2 PATHFINDER study with 2-year follow-up. Poster P1023. European Hematology Congress, June 8-15.* 2023.	Thank you for your comment. No action needed.

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	British Society for Haematology	No. Patients in all categories of AdvSM patients appear to have a response to Avapritinib to some degree and improved compared to data available to Midostaurin. No head to head comparisons of Avapritinib with Midostaurin or Cladrabine but indirect comparison with data from centres managing patients with advanced systemic mastocytosis suggest that there is an advantage of using Avapritinib over Midostaurin/Cladrabine with improved CR rates,overall survival and duration of responses. Refs: Pilkington et al.Fut Onc 2022. 18:1583-1594 Reiter et al.Leukaemia 2022. 36:2018-2120 A very small selected group who maybe eligible for allogenic bone marrow transplantation as a curative option may only be able to progress to BMT with a better outcome post treatment with TKI , Avapritinib as this may result in deeper responses e'g' CR/CRh but these are a small number to date.	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	The trials included ASM, SM-AHN and MCL patients and all responded to avapritinib. We do not believe, based on the data we have seen thus far, that any of these subgroups should be considered separately.	Thank you for your comment. No action needed.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed

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Comparators	Blueprint Medicines (UK) Ltd	Blueprint Medicines considers that the only relevant comparator for avapritinib is midostaurin, as it is the only treatment for AdvSM that is recommended by NICE.[21] Midostaurin is the current standard of care and constitutes established clinical practice for patients with AdvSM in England.[22] UK clinical experts have indicated that midostaurin is currently used in almost all AdvSM patients who are eligible for first-line therapy in UK clinical practice.[22] Based on expert clinical opinion, avapritinib mechanism of action as a highly selective and potent kinase inhibitor designed specifically to target the KIT D816V mutation, and clinical evidence to date, Blueprint Medicines anticipates avapritinib will be used in [redacted].[22] It is noted that treatment for AdvSM may include interferon alpha, cladribine, imatinib, nilotinib or dasatinib, however, none of these treatments are licensed for the treatment of AdvSM. Moreover, these off-label treatments do not target the driver of the disease and, due to limited and/or unproven efficacy or safety concerns, these therapies are included in the National Comprehensive Cancer Network (NCCN) guidelines as 'other recommended regimens' rather than 'preferred regimens'.[23] In the UK, cladribine may be used in some patients, in particular if rapid mast cell debulking is required, however other treatments are used more rarely and the use of nilotinib and dasatinib is negligible.[5,22] 5. National Institute for Health and Care Excellence. Midostaurin for treating advanced systemic mastocytosis [ID1573] - Committee Papers. 2020; https://www.nice.org.uk/guidance/ta728/documents/committee-papers. Accessed 28 June, 2023. 21. National Institute for Health and Care Excellence. Midostaurin for treating advanced systemic mastocytosis. 2021; https://www.nice.org.uk/guidance/ta728. Accessed 28 June, 2023.	Thank you for your comment. The scope has been updated. Midostaurin, cladribine, interferon alpha and imatinib have been kept in the scope as potential comparators. The technology appraisal committee will consider all evidence when deciding on appropriate comparators

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		22. Cogentia BM. *Strategic market access advice for avapritinib in the UK; HCP validation regarding positioning and comparators for avapritinib [DATA ON FILE].* 2022. 23. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guidelines). Systemic mastocytosis. 2022; https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.	
	British Society for Haematology	Only relevant comparators are: • Midostaurin - Main comparator as TKI and same class of drug – C-KIT inhibition as part of mechanism. Gotlib et at.NEJM.2016;374:2530-41 • Cladrabine - Second comparator as was 1st line pre Midostaurin approval. Cytoreductive rather than targeted agent and leads to mast cell disease burden reduction in patients who are in need to rapid debulking of disease. Not disease modifying. Dasatanib - not used and shown to be ineffective – so not a comparator Imatinib - Only approved in rare -CKIT negative SM cases or in a rarer subtype of well differentiated SM (WDSM) which make up < 5% of SM cases. Not a comparator Ref: Alvarez-Twose etal. Oncotarget, 2017;8:68950-68963 Interferon alpha - Not for AdvSM – In my clinical experience of 16 years I never prescribed this. Not disease modifying and no place since the TKI era – since Midostarurin has been approved. Nilotinib - not used and shown to be ineffective – so not a comparator	Thank you for your comment. The scope has been updated. Midostaurin, cladribine, interferon alpha and imatinib have been kept in the scope as potential comparators. The technology appraisal committee will consider all evidence when deciding on appropriate comparators
	The UK Mastocytosis Support Group	We have consulted with the five UK haematologists who treat the most UK AdvSM patients. They agree that nilotinib and dasatinib are no longer in use for AdvSM. (Indeed, in our joint submission for the midostaurin assessment	Thank you for your comment. The scope has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
	and Leukaemia Care (joint submission)	we made the same comment because it was already clear that they were not of value in this patient population.) Interferon alpha is also no longer an appropriate treatment in advanced mastocytosis where midostaurin is available. Interferon alpha was commonly used before midostaurin was available (and before trials for avapritinib were available) because it can improve symptoms in some patients, but it does not target the underlying problem of mast cell proliferation as midostaurin and avapritinib do. It is occasionally used as an accompaniment to tyrosine kinase inhibitor (TKI) cytoreductive therapy where there is osteoporosis but not in place of a TKI. (Casassus P et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. Br J Haematol. 2002 Dec;119(4):1090-7.) Imatinib is only used in patients without the very common D816V mutation in the KIT receptor (~5% of patients (Pardanani A. Am J Hematol. 2023 Jul;98(7):1097-1116)) because D816V mutated mast cells are resistant to imatinib. Avapritinib's indication is advanced mastocytosis regardless of mutation status, so imatinib would only be considered a comparator for a small portion of this population, as with midostaurin. Cladribine is a broader cytoreductive therapy whose use has changed in advanced mastocytosis now that midostaurin is available (and similarly for patients who have had compassionate access to avapritinib). According to leading one leading UK haematologist we polled, it is now more limitedly used in patients who present with extensive infiltration of the spleen or other organs to "debulk" as a first step. Because it is not a targeted therapy it would likely then be then followed by a TKI, which can bring about sustained positive changes in the bone marrow and affected organs (and in avapritinib a complete clearing of these organs and reversal of damage in some patients). It might also be used in place of a TKI in the occasional patient who has	Midostaurin, cladribine, interferon alpha and imatinib have been kept in the scope as potential comparators. The technology appraisal committee will consider all evidence when deciding on appropriate comparators.

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		cardiac issues that preclude use of a TKI (so, as an alternative to either midostaurin or avapritinib). It might also be used in a patient who presents with thrombocytopaenia, until platelet counts have risen to a level where midostaurin or avapritinib is appropriate. Another leading haematologist wrote: "'I have only used cladribine once (many years ago) with minimal response, and in the era of targeted therapy I think its role is very limited. Given access to midostaurin (and hopefully in due course, to avapritinib) I can't see any circumstance when I'd opt for cladribine, even in cases with heavy organ infiltration. It's very immunosuppressive and non-selective, with very limited data for efficacy." **Midostaurin** is the most direct comparator because it is in a similar class of medications (TKIs) and is designed to target the mutated mast cells in advanced mastocytosis as avapritinib is. Like avapritinib (in compassionate use and in other countries where it is approved) midostaurin is being used as initial treatment or occasionally after debulking with cladribine.	
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed
Outcomes	Blueprint Medicines (UK) Ltd	Blueprint Medicines agrees that the outcomes listed in the draft scope are appropriate and generally aligned with those assessed in the key trials.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology	YES these seem appropriate The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life – to include validated PROs used in trials in addition	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	The list of outcomes is appropriate. In the Questions for Consultation, you asked if "symptom severity" should be included as an outcome. As this data is available from the trials for avapritinib and as the symptoms in advanced systemic mastocytosis have a significant negative effect on quality of life, we think this would be a helpful addition to the list of outcomes.	Thank you for your comment. Symptom severity has been added to the scope as an outcome.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	Overall health-related quality of life is very important, and it comprises several aspects including symptomatic improvement, adverse effects of treatment, and a broad psychosocial impact of the condition and its treatment. Adverse effects of treatment is (rightly) included, but the other major aspect of quality of life is the symptomatic impact of AdvSM. In clinical practice symptoms are often disproportionate to investigation findings, so while we aim for measurable improvements in laboratory or imaging findings much of what patients view as important relates to symptom severity. There are some strategies available to help treat acute or chronic mediator-release symptoms but these are limited. Symptom improvement was included in the avapritinib trials, and it is approved by the FDA for symptomatic treatment of Indolent SM, and symptom control in AdvSM is no less important than in ISM.	Thank you for your comment. Symptom severity has been added to the scope as an outcome.
Equality	Blueprint Medicines (UK) Ltd	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.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		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.[24] 24. 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.	
	British Society for Haematology	I don't think there will be any exclusions I don't think there will be any differential access I don't think there will be any adverse impact	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	We do not know of any specific equality related concerns that should be considered in regard to avapritinib.	Thank you for your comment. No action needed.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Blueprint Medicines (UK) Ltd	No comment	No action needed.
	British Society for Haematology	Please review updates references suggested re: trial data/ comparator data/patient surveys re: unmet need.	Thank you for your comment. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	Advanced systemic mastocytosis is very rare. These patients are as deserving of quality care as any other patients in the UK, and in principle should have options for their treatment if those options exist and even more so in this case where the outcome data for this new drug is better than for existing treatments. These patients suffer not only from the kinds of constitutional symptoms experienced by patients with other myeloproliferative diseases, but also with symptoms of mast cell activation in many cases, including anaphylaxis, as well as sensitivity to foods, inhalants (cleaners, perfumes, alcohol), wasp venom, etc. Life can be extremely difficult and there is significant unmet need with existing approved treatments.	Thank you for your comment. No action needed.
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Blueprint Medicines (UK) Ltd	**Are the outcomes listed appropriate? Should change in symptom severity be included as an outcome?** As described in the 'Outcomes' section above, Blueprint Medicines agrees that, while the outcomes listed are appropriate and generally aligned with the key clinical trials, symptom severity could be included as an outcome. In the key phase 2 trial, PATHFINDER, symptom severity is captured via the AdvSM Symptom Assessment Form (AdvSM-SAF). **Are the subgroups listed appropriate? Are there any other subgroups of people in whom avapritinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As described in the 'Subgroups' section above, Blueprint Medicines believes that the subgroups stated in the draft scope are appropriate, however, comparative evidence might be challenging due to limited data from the comparator (midostaurin). **Where do you consider avapritinib will fit into the existing care pathway for advanced systemic mastocytosis?** As per previous engagements with clinical experts in the UK, avapritinib is expected to be used [redacted]. The general consensus from interviews with five consultant haematologists in the UK was that, based on available clinical evidence and experience, avapritinib would be used as [redacted].[22] 22. Cogentia BM. *Strategic market access advice for avapritinib in the UK; HCP validation regarding positioning and comparators for avapritinib [DATA ON FILE].* 2022. **Would avapritinib be a candidate for managed access?**	Thank you for your comment. Symptom severity has been added to the scope as an outcome. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Blueprint Medicines does not believe that avapritinib would be suitable for managed access. 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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** As noted in the midostaurin assessment, AdvSM is typically a debilitating disease, which often affects people of a working age necessitating that they stop working. Family members often become carers for these patients and as such, AdvSM is often a big source of stress and anxiety for patients, their families and their carers. However, impact on caregiver quality of life is unlikely to be included in the QALY calculation. **<u>Cost-comparison process</u>** **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?** There are no head-to-head studies comparing avapritinib and midostaurin, and the evidence base for both treatments consists of single-arm phase II trials. However, results from indirect treatment comparisons indicate that avapritinib may provide improved clinical effectiveness compared with midostaurin: • In an external control study comparing patients treated with avapritinib in the EXPLORER and PATHFINDER studies to patients treated with	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. Cost comparison has been deemed not

Section	Consultee/ Commentator	Comments [sic]	Action
		best available therapy, which includes midostaurin, in a multi-centre, observational, retrospective chart review study, a significant benefit was observed with avapritinib, in terms of overall survival and treatment duration.[11] • Results from a matching-adjusting indirect treatment comparison to estimate the relative efficacy of avapritinib compared with midostaurin suggest that avapritinib improves survival and response rate compared with midostaurin, including the subgroup of avapritinib-treated patients who were midostaurin treatment naïve.[10] Avapritinib is likely to be similar to midostaurin in terms of drug acquisition cost and resource use. It is expected that a [redacted] for avapritinib will be submitted as part of this appraisal, if considered via the cost comparison route. Both avapritinib and midostaurin are administered orally (once per day and twice per day, respectively, for the treatment of AdvSM). The adverse events profile of midostaurin and avapritinib differ.[25,26] However, based on the frequency of adverse events observed in the respective clinical studies, preliminary modelling has shown the difference in resource use cost to the NHS for management of adverse events is estimated to be minimal over a patient's lifetime. 10. Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. *Future Oncol.* 2022;18(13):1583-1594. 11. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia.* 2022;36(8):2108-2120. 25. European Medicines Agency. *Avapritinib SmPC (summary of product characteristics) EPAR.* 2022.	appropriate. This topic will be routed through the Single Technology Appraisal route.

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		26. Electronic medicines compendium. Midostaurin UK SmPC (summary of product characteristics). 2022; https://www.medicines.org.uk/emc/product/9134/smpc#gref **Will the intervention be used in the same place in the treatment pathway as the comparator(s)?** [redacted] The general consensus from interviews with five consultant haematologists in the UK was that, based on available clinical evidence and experience, avapritinib would be used [redacted].[22] • Avapritinib has increased potency compared to midostaurin. While midostaurin has demonstrated activity against KIT D816V in vitro, this activity has been shown to be approximately 10 times lower compared to avapritinib.[27] • Results from a matching adjusted indirect treatment comparison and an external control study indicate that avapritinib provides improved health benefits compared with midostaurin, and best available care, that included midostaurin, respectively.[10,11] • Avapritinib is expected to increase eligibility for HSCT, given that treatment allows some patients to achieve complete remission (CR). CR/ complete remission with partial haematologic recovery (CRh) were seen for 27% (n=22/83) of patients in the pivotal single-arm phase II PATHFINDER trial receiving avapritinib based on the 2-year data cut (September 2022).[20] In treatment-naïve patients 40% (n=12/30) of these patients achieved CR or CRh. • Avapritinib is generally well tolerated, with the majority of adverse events (AEs) in clinical trials being grade 1 or grade 2.[20,28,29] Compared to other best-available therapies for AdvSM, patients who receive avapritinib remain on treatment for longer.[11]	Thank you for your comment. Cost comparison has been deemed not appropriate. This topic will be routed through the Single Technology Appraisal route.

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		10. Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. *Future Oncol.* 2022;18(13):1583-1594. 11. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia.* 2022;36(8):2108-2120. 20. Gotlib J, Reiter A, Radia D, Deininger M, George T. *Avapritinib in patients with advanced systemic mastocytosis (AdvSM): Efficacy and safety analyses from the phase 2 PATHFINDER study with 2-year follow-up. Poster P1023. European Hematology Congress, June 8-15.* 2023. 28. DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. *Nat Med.* 2021;27(12):2183-2191. 29. Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. *Nat Med.* 2021;27(12):2192-2199. **Have there been any major changes to the treatment pathway recently? If so, please describe.** No, Blueprint Medicines are not aware of any major changes to the treatment pathway. **Will the intervention be used to treat the same population as the comparator(s)?** Yes, based on feedback from five consultant haematologists in the UK, avapritinib is expected to be used to treat the same population as midostaurin, for the treatment of AdvSM.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Overall is the technology likely to offer similar or improved health benefits compared with the comparators? Yes, avapritinib is likely to offer improved health benefits compared to midostaurin: • Results from an indirect treatment comparison indicate that avapritinib may provide improved health benefits compared with midostaurin, including improvements in overall survival, objective response rate and complete remission.[10] • An analysis of patients treated with avapritinib compared with patients treated with best available therapy, which includes midostaurin, also indicated significantly improved survival with avapritinib.[11] • Avapritinib is expected to increase eligibility for HSCT, given that treatment allows some patients to achieve complete remission or complete remission with partial haematologic recovery.[20] • Avapritinib is generally well tolerated, and in an analysis with an external control study patients were able to remain on therapy for longer in comparison to a cohort treated with other available therapies, which included midostaurin.[11,20,28,29] 10. Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. *Future Oncol.* 2022;18(13):1583-1594. 11. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia.* 2022;36(8):2108-2120. 20. Gotlib J, Reiter A, Radia D, Deininger M, George T. *Avapritinib in patients with advanced systemic mastocytosis (AdvSM): Efficacy and safety analyses from the phase 2 PATHFINDER study with 2-year follow-up. Poster P1023. European Hematology Congress, June 8-15.* 2023.	Thank you for your comment. No action needed. Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		28. DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. *Nat Med.* 2021;27(12):2183-2191. 29. Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. *Nat Med.* 2021;27(12):2192-2199. **Would it be appropriate to use the cost-comparison methodology for this topic?** Yes, Blueprint Medicines believes that a cost comparison evaluation is the appropriate route to establish the clinical and cost effectiveness of avapritinib for the treatment of AdvSM. Midostaurin is the only treatment recommended by NICE for the treatment of AdvSM in adults.[21] Based on feedback from five consultant haematologists in the UK,[22] midostaurin is currently used as first line therapy for patients with AdvSM who require disease-modifying therapy (except in cases of AdvSM-AHN where an associated neoplasm requires more immediate treatment). Avapritinib is expected to be used [redacted]. Avapritinib is anticipated to be similar to midostaurin in terms of drug acquisition cost and resource use. Moreover, the results of indirect treatment comparisons indicate that avapritinib may provide improved health benefits compared with midostaurin. 21. National Institute for Health and Care Excellence. Midostaurin for treating advanced systemic mastocytosis. 2021; https://www.nice.org.uk/guidance/ta728. Accessed 28 June, 2023.	Thank you for your comment. Cost comparison has been deemed not appropriate. This topic will be routed through the Single Technology Appraisal route.

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		22. Cogentia BM. *Strategic market access advice for avapritinib in the UK; HCP validation regarding positioning and comparators for avapritinib [DATA ON FILE].* 2022.	
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	**Are the outcomes listed appropriate? Should change in symptom severity be included as an outcome?** Answered above. **Are the subgroups listed appropriate? Are there any other subgroups of people in whom avapritinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Answered above. **Where do you consider avapritinib will fit into the existing care pathway for advanced systemic mastocytosis?** Based on discussions with UK haematologists, we conclude that avapritinib would likely be used in advanced systemic mastocytosis patients with end organ damage who are now offered midostaurin as first line therapy and particularly in those who have higher risk factors (additional mutations that indicate a poor prognosis), or in patients for whom midostaurin is no longer working/tolerated. It is likely that it would be offered as first line in patients whose platelets are over 50 x10(9)/L because the trial data shows that it is more effective in patients who have not previously had midostaurin. (ORR 83% v 59%; CR/CRh rate 44% vs 18% in one study (DeAngelo DJ, et al. Nat Med. 2021;27(12):2183-2191*)).* Trial and real-world data show responses in avapritinib are quicker and deeper than in midostaurin, and it is generally well tolerated (with side effects being reversible with lower doses where needed). Midostaurin and avapritinib are the only treatments that are disease modifiers so would be preferred over cladribine (only used for debulking or where a TKI cannot be used) or interferon (used occasionally for management of	Thank you for your comment. No action needed Thank you for your comment. No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
		osteoporosis) or imatinib (used only in the small percentage with a suitable mutation). **Would avapritinib be a candidate for managed access?** The existing trial data is compelling, so we do not see an additional benefit from a managed access arrangement. **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?** Avapritinib may expand access to bone marrow transplant because it may achieve a CR of the mastocytosis component of the disease (in some patients) which can set the stage for more successful BMT. Midostaurin does not have this additional benefit because it does not lead to CR. As BMT can be curative, it may decrease cost over the lifetime of a patient vs. ongoing treatment with a TKI. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The Explorer and Pathfinder trials of avapritinib show evidence of CR and CRh (complete remission with partial haematologic recovery (residual cytopenias permitted)) in 32% of all AdvSM patients and similar in SM-AHN patients, who are most likely to be candidates for BMT (and are approximately 70% of AdvSM patients). There are cases that are not yet published of use of avapritinib in the lead up to successful BMT that we have heard about from discussions with haematologists. **NICE is considering evaluating this technology through its cost comparison evaluation process.** **Please provide comments on the appropriateness of appraising this topic through this process.** • **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators?** In the trials (cited above) and in the ASH poster sharing data on a group of UK patients	Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
		using avapritinib on compassionate use, the clinical effectiveness was better than in midostaurin. From discussions with UK haematologists we conclude that monitoring and other management of patients is likely to be similar for avapritinib and midostaurin. **Or in what way is it different to the comparators?** UK haematologists report that avapritinib is generally better tolerated than midostaurin in their experience (in patients with platelets above 50 x10(9)/L). • **Will the intervention be used in the same place in the treatment pathway as the comparator(s)?** Yes. **Have there been any major changes to the treatment pathway recently? If so, please describe.** According to the UK haematologists we consulted, the addition of midostaurin in 2021 has been the major recent change in the pathway. Access to trials have also altered the decision-making for clinicians, as well as a short period of compassionate use access to avapritinib outside of trials. • **Will the intervention be used to treat the same population as the comparator(s)?** Yes, according to the five haematologists we consulted. • **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** Improved health benefit. From one of the haematologists we consulted: "I would expect avapritinib to offer improved health benefits compared to midostaurin (improved efficacy, potentially less toxicity)."	Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed Thank you for your comment. No action needed

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Would it be appropriate to use the cost-comparison methodology for this topic?** Neither charity has experience with this methodology and we are not in a position to comment about the appropriateness of the approach.	
	British Society for Allergy and Clinical Immunology / Joint Committee on Immunology and Allergy	No comment.	No action needed
Additional comments on the draft scope	Blueprint Medicines (UK) Ltd	Please add the mechanism of action for avapritinib to the technology section, in line with the NICE scope for midostaurin for advanced systemic mastocytosis. Avapritinib is a highly selective and potent kinase inhibitor which was designed specifically to target the KIT D816V mutation.	Thank you for your comment. The mechanism of action is no longer included in NICE scopes. No action needed.
	The UK Mastocytosis Support Group and Leukaemia Care (joint submission)	There is significant unmet need in the advanced systemic mastocytosis population. As this may be the only opportunity to share a patient perspective, if avapritinib goes through the cost comparison route, we hope you won't mind if we share (with permission) the following from a patient diagnosed with SM-AHN (CMML that is currently well controlled):	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		"Before I got treatment I had no energy and found it difficult to do anything at all. I had very blotchy and itchy skin on my back and front plus bouts of diarrhoea and urine infections. I first went to the doctor in July 2018 about my constant urine infections and a persistent cough that wouldn't shift despite endless courses of antibiotics. My doctor finally sent me for a scan in August 2020 and I was diagnosed in October. Having been diagnosed in October [my consultant] was keen to get me on avapritinib and I finally got it at the end of March 2021. [The consultant] gave me some steroids in the meantime to try and give me more energy. Taking the avapritinib for me was miraculous, the constant itching stopped almost immediately and my symptoms gradually subsided. I still get tired, and it takes me a while to get going in the mornings although this is slowly improving. I was running my own business, but I have now retired, having the disease definitely forced the issue but I am nearly 68 now. I always enjoyed my sport and am now slowly building up my strength again. I now enjoy gardening and socialising again plus going away in my campervan!"	
	British Society for Allergy and Clinical Immunology / Joint Committee	Our experts note that avapritinib is being included in existing care pathways as an alternative to midostaurin where midostaurin is contraindicated or not tolerated.	Thank you for your comment. Avapritinib will be considered within its marketing authorisation. The

Section	Consultee/ Commentator	Comments [sic]	Action
	on Immunology and Allergy		technology appraisal committee will consider all evidence when deciding on appropriate comparators.

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

None