National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Midostaurin for treating advanced systemic mastocytosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Novartis Pharmaceuticals	The wording of the remit appropriately reflects the clinical and cost-effectiveness issues that NICE should consider.	Comment noted. No change to scope required.
	Genetic Alliance UK	The wording of the remit matches the standard format.	Comment noted. No change to scope required.
	RCPath and BSH	Yes	Comment noted. No change to scope required.
	The UK Mastocytosis Support Group	Yes	Comment noted. No change to scope required.

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Timing Issues	Novartis Pharmaceuticals	Advanced systemic mastocytosis comprises a number of rare heterogeneous haematologic neoplasms that are associated with poor prognoses and a lack effective treatment options[1]. As such, this topic is highly appropriate and urgent given that no treatments for advanced systemic mastocytosis have been previously assessed by NICE and midostaurin has demonstrated considerable benefits for patients[1].	Comment noted. This appraisal has been scheduled in the work programme.
	Genetic Alliance UK	Midostaurin is the only technology with a marketing authorisation to treat the condition. Given the seriousness of the condition it is therefore appropriate that the medicine be appraised quickly in order for patients who would benefit from the treatment to gain access as soon as possible.	Comment noted. This appraisal has been scheduled in the work programme.
	Leukaemia Care	There are no treatments current licensed for this condition, so this is a particularly urgent application for those with this indication. Those with the rarest form, mast cell leukaemia, have a median survival time of less than 6 months. Additionally, this treatment has been licensed in the UK, for this indication, since September 2017, meaning NICE has missed the target of appraising the treatment within 90 days of licensing. Patients have been without this treatment for almost 2 years and will have to wait an additional 18 months, assuming the appraisal is successful. Therefore, we would like to stress the urgency of this appraisal.	Comment noted. This appraisal has been scheduled in the work programme.
	RCPath and BSH	No good alternatives	Comment noted. This appraisal has been scheduled in the work programme.

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	The UK Mastocytosis Support Group	There are no other medications in the UK that are approved for use in advanced forms of mastocytosis, and the drugs that are being used are not as effective as midostaurin for many patients. While Novartis is continuing to provide the drug to patients who were on it before it was given marketing authorisation by the EMA in 2017, new patients have access only through an IFR, and not all haematologists are equally adept at applying for the IFR (and not all requests may be approved). As this is a life-extending drug in a condition with no other drug that performs nearly as well, there is an urgent need for NICE to assess midostaurin. There is an additional negative consequence of the current funding situation for midostaurin, that affects all mastocytosis patients. Patients who are currently taking midostaurin are (sensibly) unwilling to stop taking it in order to enter trials for new tyrosine kinase inhibitors because they are wary of losing their compassionate use status should they want to return to midostaurin. We have seen evidence that this has had an effect on recruitment for the two promising TKI trials that are happening in the UK at present.	Comment noted. This appraisal has been scheduled in the work programme.
Additional comments on the draft remit	Genetic Alliance UK	This treatment has been selected for a STA, though: - the treatment is expected to be licensed for an estimated ~570 individuals, - it is clinically distinct - it is chronic and severely disabling (can cause death within six months), Thereby meeting many of the criteria for the Highly Specialised Technology Evaluation Programme. There is no highly specialised service commissioning arrangement for this condition. This is likely to be the reason the technology has not been	Comment noted. This topic does not meet the criteria for consideration as a highly specialised treatment. The treatment is not expected to be used exclusively in the context of a highly specialised service. This is because it is also used to treat FLT3-

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		proposed for an evaluation under the Highly Specialised Technology programme. Genetic Alliance UK believe that the need for national commissioning of the technology is significant, but until the technology under consideration is available it is unlikely to be granted. There appears to be flaw in access to HST evaluation for conditions where a service would be built around a life-saving treatment, but would otherwise lack much intervention. We propose that an exception to this requirement be made for the purposes of this evaluation.	positive acute myeloid leukaemia, and because mastocytosis is not currently managed in a highly specialised service.

Comment 2: the draft scope

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Background information	Novartis Pharmaceuticals	The background information states that the aim of treatment is to decrease the number of mast cells. Please expand to include that the aim of treatment is also to control symptoms, thus treatment is highly individualised based on the symptoms experienced and other biological factors. It is also noted that treatment for advanced systemic mastocytosis may include interferon alpha, cladribine, imatinib, nilotinib or dasatinib. Please add that none of these treatments are licensed for this indication.	Thank you for your comment. The scope has been updated. The scope states that the treatments listed do not currently have a marketing authorisation in the UK for this indication.
	Genetic Alliance	According to SS Cohen *et al*., (ncbi.nlm.nih.gov/pubmed/24761987) and JJ van Doormal *et al*., (jacionline.org/article/S0091-6749(12)01660-0/abstract)	Thank you for your comment. The

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		the prevalence of systemic mastocytosis is closer to 1/10,000. The prevalence of the advanced form is thought to be 10% of the systemic mastocyctosis population.	background section of the scope has been updated.
	RCPath and BSH	Yes	Comment noted. No change to scope required.
	The UK Mastocytosis Support Group	There are newer estimates of the prevalence of mastocytosis than the ones you've cited. Two newer estimates are based on data collected in countries with very well-delineated catchment areas for the specialist centres. A study from Denmark estimates that the prevalence of all forms of systemic mastocytosis is 9.6 per 100,000. (Cohen SS et al, **Epidemiology** of systemic **mastocytosis** in **Denmark**. Br J Haematol. 2014 Aug;166(4):521-8). Of those, 6.8 percent had advanced forms of mastocytosis—which puts the prevalence of the advanced forms at 0.65 per 100,000. A second study that looks only at indolent and smouldering SM estimated the prevalence at 13 per 100,000. (van Doormaal JJ et al, ***Prevalence*** of indolent ***systemic mastocytosis*** in a Dutch region. J Allergy Clin Immunol. 2013 May;131(5):1429-31.) Studies vary in their estimates of the relative number of indolent/SSM patients to those with advanced SM. While the Cohen paper above found 6.8% of all SM patients with advanced forms, the registry of the European Competence Network on Mastocytosis (ECNM) as of 2018 had 18% with advanced forms of SM (of 3,000 patients). (Valent et al, ***The Data Registry of the European Competence Network on Mastocytosis (ECNM): Set Up, Projects, and Perspectives, JACI*** Volume 7, Issue 1, January 2019, Pages 81-87. If we assume that van Doormal et al are correct and there are 13 ISM/SSM patients per 100,000	Thank you for your comment. The background section of the scope has been updated.

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		population, and the ECNM have the proportions right (with Advanced SM at 18% of the total SM population), then the prevalence of advanced SM could be as large as 2.9/100,000. So, perhaps between .65 and 2.9 per 100,000 for advanced patients. In addition, though the NHS website that you cite lists nilotinib and dasatinib as treatments, it is our understanding that neither are being used with any frequency in the UK (or elsewhere) because trials have not shown sufficient efficacy, and midostaurin has better results and has been available to some patients (still on compassionate use or through IFR). Interferon alpha, cladribine and imatinib (for those without the D816V KIT mutation) are still used. Hydroxyurea (which is not specific to mast cells) is also used, though primarily for SM-AHN where there is another haematologic neoplasm alongside the mastocytosis or occasionally to debulk mast cells.	
The technology/ intervention	Novartis Pharmaceuticals	The description of the technology is accurate, however please note that midostaurin is also indicated for adult patients with newly diagnosed acute myeloid leukaemia (AML), fit for intensive chemotherapy, and with a FLT3 mutation[2,3,13]	Comment noted. No change to scope required.
	RCPath and BSH	Yes	Comment noted. No change to scope required.
	The UK Mastocytosis Support Group	You do not specify the dose at which it is used, but we know that there is some variation in the dose used, with some long-term patients using a lower than standard dose. That should be taken into consideration on the cost side.	Comment noted. The scope is intended to give a brief summary of the technology only. The dose and cost of treatment will be taken

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			into account throughout the appraisal process.
Population	Novartis Pharmaceuticals	Advanced systemic mastocytosis (Adv SM) is a rare heterogeneous disease that affects between 1 in 20,000 and 1 in 40,000 people worldwide[4]. Advanced systemic mastocytosis comprises of 3 different subtypes, each associated with very different outcomes[4,5]: • Aggressive systemic mastocytosis (ASM), which accounts for ~5-10% of SM cases and has a life expectancy ~3.5 years • Mast cell leukemia (MCL), which accounts for ~1% of SM cases and has a life expectancy ~<6 months • SM with an associated hematologic neoplasm (SM-AHN), which accounts for ~20-30% of SM cases and has a life expectancy ~2 years Therefore the description of the population is accurate and is consistent with the CPKC412D2201[1] trial (the pivotal study for this assessment). Note that the CPKC412D2201[1]: is a single arm, phase II open-label study of midostaurin in the described population. The population in the trial is extremely heterogeneous with very limited patient numbers for each subgroup of patients, and given the paucity of data available in this indication (n = 89), subgroup analysis will be dependent on the available evidence base.	Comment noted. The scope has been updated to include consideration of subgroups by disease type if evidence allows.
	RCPath and BSH	Yes	Comment noted. No change to scope required.
	The UK Mastocytosis Support Group	The population has been defined appropriately given that Midostaurin is a multi-targeted kinase inhibitor (and therefore might be considered for patients with and without the most common mutation in KIT). There was a response	Comment noted. No change to scope required.

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		in all three variants for which it received marketing authorisation and all should be included in this assessment.	
Comparators	Novartis Pharmaceuticals	Currently, there are no UK specific clinical guidelines for advanced systemic mastocytosis (the only available guidelines are from the USA - National Comprehensive Cancer Network- NCCN[15]) and midostaurin is the only therapy licensed in the UK for this indication. UK guidelines are in development, and are expected to be rolled out within 18 months[16] Current treatment options include therapies as described in the draft scope (cladribine is most commonly used, interferon and imatinib (for disease without the CKIT D816V mutation) are used in approximately 5% and we understand that nilotinib and dasatinib are occasionally used), however the evidence base for these treatments is very limited. Hydroxyurea or cytarabine are also used for this indication with hydroxyurea as an initial cytoreductive therapy in ASM and cytarabine for aggressive induction in MCL or SM-AHN. Transplantation is the only curative treatment option, but is very rarely used in MCL and SM-AHN with less than 5% of patients undergoing transplantation[16]	Thank you for your comment. As discussed at the scoping workshop, stem cell transplant, hydroxyurea and cytarabine have not been added to the scope because they are unlikely to be used to treat the mastocytosis, as midostaurin would be. No change to the scope.
	Leukaemia Care	All possible comparators listed should be compared, as none are licensed or recommended as standard of care.	Comment noted. No change to the scope.
	RCPath and BSH	No	Comment noted. The comparators were discussed at the scoping workshop and the scope has been left broad with regard to comparators to take into

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			account the variety of treatments that may be given for mastocytosis.
	The UK Mastocytosis Support Group	Several factors lead to some diversity in treatment approach in the UK (and indeed in the rest of Europe and the US). There is no other drug approved for the treatment of mastocytosis and no care pathway in the UK (though the development of one has recently begun), there is also no full consensus in the research community on the optimal single comparator treatment (though now there is a consensus that midostaurin in best the starting point for many patients). We know this is wrestled with in study design for other trials for mastocytosis. There is diversity within the patient population (three variants ASM, SM-AHN, and MCL) with different life expectancies and co-morbidities such that it is difficult to identify a standard treatment. Patients with SM-AHN may also be receiving treatment for their other haematologic neoplasm. We consulted with the two leading haematologists treating mastocytosis in the UK about their own practice. Both said that in their practices the appropriate comparators would be interferon alpha (with or without prednisolone), cladribine (2-CdA), and imatinib (in patients without the typical D816V mutation, which is a very small percentage of patients). Allogeneic Hematopoetic Stem Cell Transplant is also used in some patients who qualify and have a donor match. Neither of these doctors use nilotinib or dasatinib at present, and this is consistent with the research literature as well. (e.g. Theoharides et al, Mast Cells, Mastocytosis, and Related Disorders, NEJM N Engl J Med 2015; 373:163-172).	Comment noted. The comparators were discussed at the scoping workshop and the scope has been left broad with regard to comparators to take into account the variety of treatments that may be given for mastocytosis.

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		An article that lays out the views on treatment from the leading world experts on mastocytosis is consistent with UK practice. (Valent et al Advances in the classification and treatment of mastocytosis: current status and outlook toward the future, Cancer Res. 2017 Mar 15; 77(6): 1261–1270.) Here is one of our member's experience with Nilotinib for ASM (shared with the patient's permission): "I agreed to go on a 3-year trial of a drug called AMN107 (later named Nilotinib). Although the drug did somewhat alleviate the mastocytosis symptoms, the side effects were awful and 6 months later BMBs [bone marrow biopsies] were showing no decrease of abnormal cells, in fact there had been slight increase. As a result of the drug, my liver function was very compromised, I had serious fluid retention including extensive pleural effusion, constant headaches as well as other problems. [Within a year] I decided to abandon the trial and the medical staff at the [trial hospital] agreed this was the best course of action". This patient is tolerating midostaurin well. One of the doctors we consulted said Nilotinib and Dasatinib gave some patients some relief from some symptoms there was insufficient evidence that they decreased the number of mutated mast cells in the bone marrow and so were not treating the underlying problem. We believe these two drugs should be removed from the list of comparators because they are not in frequent use in the UK because of lack of efficacy.	
Outcomes	Novartis Pharmaceuticals	The outcome measures should reflect those assessed in the key trial (CPKC412D2201)[1,6]: for the intervention being appraised. As such, the primary and secondary outcomes are as follows: <u>Primary Outcomes</u>	Comment noted. The company may present additional outcomes to those in the scope in its evidence submission.

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		• **Best Overall Response** Defined as the percentage of participants who classified as confirmed responders (Major Response (MR) or Partial Response (PR))* by the adjudication of the Study Steering Committee and based on a Modified Valent Criteria. *Major response is defined as complete resolution of at least one C-Finding (clinical/laboratory finding) and no progression in other C-Findings. Partial response is defined as incomplete regression of one or more C-Finding(s) without complete regression and without progress in other C-Findings. C-Findings include cytopenias, osteolysis with pathologic fractures, hepatosplenomegaly with impaired liver function and/or ascites, and malabsorption. <u>Secondary Outcomes</u> • **Overall survival** Defined as the time from start of treatment to the date of death due to any cause. • **Progression-free survival** Defined as the time from start of treatment to the date of the first documented and confirmed progression or death due to any cause. • **Duration of response** Defined as the time from first onset of confirmed response (MR or PR) to the date of first documented and confirmed progression or death due to ASM/MCL • **Time to response**	No changes to the scope required.

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		Defined as the time from date of first study drug intake to date of first confirmed response. • **Adverse effects of treatment** • **Health-related quality of life**	
	Genetic Alliance UK	The outcome measures included are appropriate, but we would also suggest inclusion of other endpoints of importance to patients including reversal of organ damage and decreases in bone marrow mast-cell burden.	Comment noted. The company may present additional outcomes to those in the scope in its evidence submission. No changes to the scope required.
	RCPath and BSH	Yes	Comment noted. No change to the scope required.
	The UK Mastocytosis Support Group	Overall survival progression-free survival, response rate and adverse effects are all appropriate outcome measures. An additional challenge is to measure the improvement in the diverse range of symptoms these patients have. Midostaurin not only decreases the population of abberant mast cells, but also decreases the frequency with which mast cells release their chemical mediators (Valent et al, Midostaurin: a magic bullet that blocks mast cell expansion and activation, Annals of	Thank you for your comment. NICE welcomes submissions from patient groups that describe the experience of having advanced systemic mastocytosis, and receiving care and

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		Oncology 28:2367-2376, 2017) so even when the bone marrow is not fully responding, a patient's quality of life could be improving. Some patients will have symptoms related to the activation of mast cells (such as anaphylaxis, vomiting, cramping and diarrhoea, flushing) where others might have symptoms related to the presence of excess mast cells (such as pain from an enlarged spleen and or liver). Others might suffer only from fatigue from abnormalities brought on by poor bone marrow function. One patient may have explosive and unpredictable diarrhoea several times daily that has been dramatically improved by midostaurin (reported to us by a patient), but another patient has never had diarrhoea. One of our members had frequent anaphylaxis from foods and has not had any incidents since starting on midostaurin. Because all forms of mastocytosis are rare and these advanced forms are the rare forms of a rare disease, the study populations are relatively small as compared to trials for common diseases NICE is often contemplating. We can certainly provide qualitative information from patients where the clinical trials have not adequately captured it, and would be happy to work with NICE to do so.	treatment. No change to the scope required.
Economic analysis	Novartis Pharmaceuticals	The economic analysis is appropriate and consistent with the NICE reference case.	Comment noted. No change to the scope.
	RCPath and BSH	None specific	Comment noted. No change to the scope.

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	The UK Mastocytosis Support Group	We have one member of our charity who has a diagnosis of ASM and has been on midostaurin (at a varying dose) for more than twelve years. The benefits should be assessed over such a time horizon. This patient was able to continue to be in paid work for a number of years and then provided childcare for her grandchildren so that the parents could be in full time work.	Comment noted. As stated in the reference case, the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. No change to the scope.
Equality and Diversity	Novartis Pharmaceuticals	We would like to highlight two potential sources of inequality in relation to the appraisal of treatments for rare indications that could apply to this appraisal. These inequalities could ultimately disadvantage patients with rare diseases including the subject of this appraisal. This inequality may be manifested in two ways, the first arising due to lack of data (quantity and quality) available to inform the assessment of treatments for rare diseases, simply due to the low numbers of patients available to study, and the second being the methodology and processes by which these rare diseases are assessed. 1. <u>Lack of data (quantity and quality) available to inform the assessment of treatments for rare diseases</u> The small patient numbers affected by each rare disease, potentially comprising heterogeneous sub-populations, means that it is highly challenging to conduct robust, randomised, controlled, clinical trials	Comments noted. Because these issues do not specifically relate to protected characteristics as defined by the Equality Act 2010, these are not equality issues. However, in its decision making, the committee will take into account the rarity of advanced systemic mastocytosis and the associated difficulties in the evidence base.

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		that are considered the gold standard in terms of evidence generation. In contrast, trials for rare diseases are often small, non-comparative and open label. Consequently the evidence bases available to support the health technology assessment of rare diseases are relatively limited and are associated with considerable uncertainty. This means that rare diseases assessed via the Single Technology Appraisal (STA) process are at a disadvantage when compared to medicines for more common diseases where more robust evidence packages are possible. Patients with rare diseases are therefore at a disadvantage as the greater uncertainty may make decision-makers less likely to approve the treatments, with the manufacturer not being able to provide the product at a sustainable price. This latter point is especially pertinent when the rare disease is a second indication – where the first indication has been deemed cost-effective by the HTA body. This is because a manufacturer may be able to give an extremely large discount on the second indication to enable patient treatment – but the inability to price differently for the 1st and second indication means that this very large discount would not be sustainable across both indications. This will result in an inequality of access to medicines for rare and non-rare diseases. 2. <u>Attitudes, methods and decision-making criteria differ between Highly Specialised Technology (HST) appraisals and STA's.</u> The current HST process was specifically designed for the evaluation of technologies for rare diseases, taking into consideration broader decision-making criteria in comparison to the conventional STA process. However eligibility for being appraised via the HST route includes the need to be used exclusively in the context of a highly specialised service. In the case where a medicine is already licensed	

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		for another indication the rare indication would be appraised under the STA rather than the HST process. This establishes an inequality in that a decision based on the HST process may be different to that resulting from the STA process, thereby disadvantaging patients with rare diseases if appraised via the STA route. In January of this year Novartis asked the NICE Office of Market Access to organise a meeting to discuss the challenges in assessing midostaurin in advanced systemic mastocytosis. [redacted] The purpose of the meeting was to seek to co-create patient access solutions for specific treatments that are not well suited to available funding routes such as midostaurin for Adv SM. Novartis were informed by NICE that the STA route would be the most appropriate route for midostaurin in advanced systemic mastocytosis since this is not the only indication for this medicine (midostaurin for untreated FLT3-mutation-positive AML received a positive reimbursement decision in June 2018). However, if advanced systemic mastocytosis was the only indication for midostaurin, it is very likely that it would be assessed under the HST process rather than the STA process, potentially leading to a different decision. As such, patients are further disadvantaged if the medicine for their rare disease has benefits beyond the rare indication in question. This constitutes an inequality in the system.	
	RCPath and BSH	No issues	Comment noted.

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	The UK Mastocytosis Support Group	We do not have any particular concerns in this area beyond concerns regarding access to care in regions that are less well served by knowledgeable consultants. We believe that patients in less well-served areas will be in a better position to get access to good care if Midostaurin is funded by the NHS because at present the patients who have access to this preferred drug are those who have access to doctors who are experienced in Individual Funding Requests.	Comment noted. Because this issue does not specifically relate to protected characteristics as defined by the Equality Act 2010, it is not an equality issue. However, the committee can take issues with access into account in its decision making.
Other considerations	Novartis Pharmaceuticals	Novartis would like to re-iterate that advanced systemic mastocytosis is a rare disease, and as is usually the case for rare diseases, there are limited clinical and comparative data available. The clinical data supporting the assessment of midostaurin in this indication comes from a single arm, phase II, open-label study that reflects the heterogenous subgroups of Adv SM patients. We would like to highlight our concerns regarding the challenges of assessing a product of this nature via the STA process. We hope that by making this submission the challenges of assessing treatments via the STA route will be highlighted and overcome, preferably as they arise. We look forward to working collaboratively with NICE and NHSE on this appraisal to find solutions that may also be applied to the assessment of other treatments for rare diseases to enable access for patients.	Comment noted. No change to the scope required. The committee can take into account the scarcity of the data in its decision making through the STA process.

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	The UK Mastocytosis Support Group	In our experience, patients with advanced forms of mastocytosis are rarely able to work. We do have some members who have been able to return to work once starting midostaurin. Most patients would otherwise be receiving disability payments if they are of working age. We do not have existing data to answer this question, but it is a question that could perhaps be asked of UK patients with advanced SM before January 2020 should that be desirable.	Comment noted. The committee welcomes submissions from patient groups reflecting the experience of patients. Please note that NICE's reference case for technology appraisal only considers costs to the NHS and personal social services.
Innovation	Novartis Pharmaceuticals	Treatments for systemic mastocytosis can be divided into two broad categories of those intended to control mast cell mediator-related symptoms (e.g. antihistamines, epinephrine, or corticosteroids) and those intended to limit the mast cell burden (e.g. cytoreductive or targeted therapies).[6,7] Due to the heterogeneous nature of the disease, treatment strategies are highly individualised and the response rates associated with current treatment options such as interferon and cladribine may be variable and short-lived with patients developing resistance.[6,7] Consequently, there is a need for effective therapies that improve disease-related symptoms, reduce disease burden, and improve survival. Midostaurin is the only treatment with a European licence for the treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm or mast cell leukaemia. A potent multi-targeted tyrosine kinase inhibitor (TKI), midostaurin inhibits a broad range of tyrosine kinases including, CKIT exon 17 (D816V) which is the	Comment noted. The committee will consider the innovative nature of midostaurin during the course of the appraisal.

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		primary driver of systemic disease and present in 80-90% of systemic mastocytosis[8,14] (D816V is also associated with clinical resistance to imatinib), inhibiting mast cell proliferation, survival and histamine release. Midostaurin also inhibits several other receptor tyrosine kinases such as PDGFR (platelet-derived growth factor receptor) or VEGFR2 (vascular endothelial growth factor receptor 2), as well as members of the serine/threonine kinase family PKC (protein kinase C) by binding to the catalytic domain and inhibiting the mitogenic signalling of the respective growth factors leading to growth arrest. [2] It is our understanding from both clinician and patient feedback that patients consider midostaurin to have substantial health benefits that significantly improve their daily ability to function.	
	Genetic Alliance UK	Midostaurin is the first technology given a market authorisation that reduces the number of mast cells rather than just tackle the symptoms of systemic mastocytosis. Given this fact it should be seen as a step change in the management of the condition.	Comment noted. The committee will consider the innovative nature of midostaurin during the course of the appraisal.
	Leukaemia Care	Given that no other treatments are licenced in the UK for this condition, this has the potential to become standard of care for these patients immediately, and so is a massive step-change in the treatment of the condition. A licensed treatment can be accessed more quickly and easily than the process for applying to access unlicensed treatment allows.	Comment noted. The committee will consider the innovative nature of midostaurin during the course of the appraisal.
	RCPath and BSH	Yes	Comment noted. The committee will consider the innovative nature of

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			midostaurin during the course of the appraisal.
	The UK Mastocytosis Support Group	This is the first targeted medication for advanced forms of systemic mastocytosis and is the first to have a significant effect on survival. It is, in our view and in the view of the clinical and research communities, is a breakthrough (e.g. Valent et al, Midostaurin: a magic bullet that blocks mast cell expansion and activation, Annals of Oncology 28:2367-2376, 2017). From the patient perspective, we have had members described going from being bed-ridden to being able to continue to work, travel and enjoy life. An ASM patient wrote the following (and it is shared with their consent): "Mainly, my SM caused episodes of crippling abdominal pain, diarrhoea and vomiting. These episodes lasted about 1 – 1 ½ hours and would occur every night and often during the day as well. I experienced reactions to some foods, loss of appetite and dramatic weight loss." This patient had fibrosis in the bone marrow and had already tried and failed Nilotinib. We wish there were extensive data on quality of life in mastocytosis, but it is not as robust as we would like it to be. However, the data that are available from Novartis from the many years of midostaurin trials include some quality of life data that should be taken into account.	Comment noted. The committee will consider the innovative nature of midostaurin during the course of the appraisal.
Questions for consultation	Novartis Pharmaceuticals	**Have all relevant comparators for midostaurin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for advanced mastocytosis?** Please refer to comments in the comparator section of this response. Although these comparators may be considered relevant in UK clinical practice, please note that any comparisons in this assessment will be dependent on the available evidence base.	Thank you for your comment. As discussed at the scoping workshop, stem cell transplant, hydroxyurea and cytarabine have not been added to the

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		The rare nature of this disease has already been discussed in this response document and a systematic literature review (SLR) conducted by Novartis in 2017[9] to identify clinical evidence on treatments for advanced systemic mastocytosis supports this position, with only (18 studies - mostly single arm non-comparative studies in heterogeneous patient populations) identified. This SLR will be updated for our planned submission in Q1 2020, however the paucity of robust clinical data in this disease area with different study populations will make cross-study comparisons challenging and lead to further uncertainty in the cost-effectiveness case. **Are the outcomes listed appropriate?** The outcomes listed in the scope are appropriate and reflect the endpoints assessed in the CPKC412D2201[1] trial **Are there any subgroups of people in whom midostaurin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As mentioned in the population section of this response, the CPKC412D2201 trial is an extremely heterogeneous phase II, single arm, open label trial (n = 89) with very limited patient numbers for each subgroup (n = 16, n = 16, and n = 57 for the ASM, MCL and SM-AHN subgroups respectively). The trial results show extremely wide confidence intervals and as such, the subgroup analysis underpinned by limited data, is associated with inherent uncertainty. For the primary endpoint, the overall response rate in the overall population was 60% (95% CI 49% – 70%) compared with 75% (95% CI 49% – 70%) in the ASM subgroup, 50% (95% CI 25% – 75%) in the MCL subgroup and 58% (95% CI 44% – 71%) in the SM-AHN subgroup[1].	scope because they are unlikely to be used to treat the mastocytosis, as midostaurin would be. No change to the scope. Comment noted. Comments noted. The scope has been updated to include consideration of subgroups by disease type if evidence allows.

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		These results are consistent with the better prognoses for patients with ASM compared with MCL and SM-AHN. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which midostaurin is licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Please refer to comments in the equality section of this response where we highlight the challenges and inequalities in the assessment of rare diseases such as advanced systemic mastocytosis. The limited evidence base with such rare diseases often leads to a higher level of uncertainty in terms of	Comments noted. Because these issues do not specifically relate to protected characteristics as defined by the Equality Act 2010, these are not equality issues. However, in its decision making, the committee will take into account the rarity of advanced systemic mastocytosis and the associated difficulties in the evidence base.

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		clinical effectiveness and for medicines such as midostaurin that are licensed for multiple indications including rare diseases there is an inequality in how these medicines are potentially assessed in the current HTA processes. **Do you consider midostaurin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition?)** Current treatments for advanced systemic mastocytosis are associated with modest and response rates and various major toxicities[10, 11]. Consequently, there is an unmet need for innovative therapies and midostaurin has the potential to meet this need, providing a step change in the management of this disease. The only treatment with a European licence for the treatment of adult patients with advanced systemic mastocytosis, midostaurin has been shown to have a favourable safety profile and be efficacious with high response rates and durable activity in patients with ASM and MCL and SM-AHN regardless of KITD816V status[1,10,11] • Overall response rate was 60% in all patients (75% in patients with ASM, 58% in SM-AHN and 50% in patients with MCL (median follow up 26 months (range 12–54)), • Median duration of response was not reached in patients with ASM or MCL and was 12.7 months in SM-AHN (median follow up 26 months (range 12–54) • Toxicities include mainly grade 1–2 gastrointestinal adverse events with grade 3–4 anemia, neutropenia and thrombocytopenia in 41%, 24%, and 29% respectively, mainly in patients with pre-existing cytopenias. [10]	Comment noted. The committee will consider the innovative nature of midostaurin during the course of the appraisal.

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		It is our understanding from patients that the benefits conferred by midostaurin will have a significant impact on their lives **Do you consider that the use of midostaurin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Adv SM 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, Adv SM is often a big source of stress and anxiety for patients, their families and their carers. Consequently, the health benefits of midostaurin on the families and carers of patients as a result of its impact on patients with AdvSM are unlikely to be captured in the QALY calculation.	Comment noted. No change to the scope. The NICE guide to the methods of technology appraisal states that all direct health benefits, whether for patients or, when relevant, carers should be included.
	Leukaemia Care	We are concerned about the choice of appraising this indication under the single technology appraisal process. The condition is extremely rare, affecting 30-90 people in the UK a year (based on the incidence as set out in the scope for all mastocytosis cases, with 1-3% of those having advanced systemic mastocytosis according to the Masto UK website). Conditions with more patients affected have been appraised previously; for example, the guidance for HST4, a treatment for Fabry disease, is estimated to applicable to 182 people. Another example would be HST9, which approved a treatment for hATTR, which was thought to be useful for 150 people. As Sir Andrew Dillon, Chief Executive of NICE stated: “NICE takes into account a greater range of criteria about the benefits and costs of highly	Comment noted. This topic does not meet the criteria for consideration as a highly specialised treatment. The treatment is not expected to be used exclusively in the context of a highly specialised service. This is because it is

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		specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair." To address this unfairness, NICE set up the Highly Specialised Technologies (HST) programme. However, this drug has been chosen to be appraised through the STA programme instead, which means it is highly likely to lead to this drug having limited or uncertain data available and a higher chance of not being approved. This indication urgently needs a form of licensed treatment, fulfilling another selection criteria of HST in that there is the need for national commissioning. Again, this is shown as the rationale for most other HST appraisals, as set out the HST topic selection document available online.	also used to treat FLT3-positive acute myeloid leukaemia, and because mastocytosis is not currently managed in a highly specialised service.
	The UK Mastocytosis Support Group	We are satisfied with the Single Technology Assessment for Midostaurin, though we believe it also meets some of the criteria for the HST route: • there is a clinically distinct population; • the disease is chronic (when treated with midostaurin vs more likely fatal without) and is very disabling; • midostaurin has the potential for life-long use; • and the need for national commissioning is significant because we believe there may be regional imbalances in access to it at present. Criteria that may not be met for the HST: • We are not aware of the proposed cost so cannot speak to whether the cost is likely to be considered "very high." • At present there are no established Centres of Excellence in the UK. We are aware of patients receiving midostaurin from five different clinics, and there may be patients we aren't aware of in the charity. If	Comment noted. This topic does not meet the criteria for consideration as a highly specialised treatment. The treatment is not expected to be used exclusively in the context of a highly specialised service. This is because it is also used to treat FLT3-positive acute myeloid leukaemia, and because mastocytosis is not currently

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		the prevalence data we cited earlier is reasonably accurate, we would estimate that there would be somewhere between 430 and 1880 patients with advanced forms of SM in the UK (though nowhere near that many are currently being diagnosed), of whom some portion would be candidates for the drug, were they actually diagnosed. At present we understand that there are tens of patients in the UK on midostaurin rather than hundreds. • There is no commissioned highly specialised service.	managed in a highly specialised service.
Additional comments on the draft scope	Novartis Pharmaceuticals	We re-iterate our earlier comments in this response document on challenges of the evidence base informing midostaurin in advanced systemic mastocytosis and the assessment via this technology via the conventional STA process. In recognition of these challenges we also re-iterate our participation in this appraisal as an opportunity for Novartis to use midostaurin as a 'test case' to further highlight and document the challenges of assessing a product of this type via the STA process rather than the NICE HST process which is arguably more suited to a product of this type. **References** 1. NEJM Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016; 374: 2530-41. 2. Novartis Pharmaceuticals UK Ltd. Tafinlar 25mg soft capsules. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/9134/smpc. [Last accessed: 10 June 2019]. 3. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009; 113: 5727-36. 4. Systemic mastocytosis. Orphanet. 2018.	Comment noted. No change to the scope required.

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		5. Gotlib J, Kluin-Nelemans HC, George TI, et al. Supplement to: Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med. 2016;374:2530-2541. 6. Protocol for: Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-41. DOI: 10.1056/NEJMoa1513098 7. Valent P, Akin C and Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017; 129: 1420–1427 8. Arock M, Sotlar K, Akin C, et al. KIT mutationanalysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015; 29(6):1223-1232 9. Novartis Systematic Literature Review. 2017 10. Vaes M, Benghiat FS, Hermine O. Targeted treatment options in mastocytosis. Front Med (Lausanne). 2017;4:110. 11. Pardanani A. et al. Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. Am J Hematol. 2016;91(11):1146–1159 12. Valent P, Akin C, Hartmann K, Nilsson G et al (2017) Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. Cancer Res 77:1261–1270. doi:10.1158/0008-5472 13. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. Blood 2013;121: 1285-95. 14. Ustun C, Arock M, Kluin-Nelemans HC, Reiter A, Sperr WR, George T, et al. Advanced systemic mastocytosis: from molecular and genetic progress to clinical practice. Haematologica (2016) 101(10):1133–43. doi:10.3324/haematol.2016.146563 15. NCCN Gotlib J, Gerds AT, Bose P, et al. Systemic Mastocytosis, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J	

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		Natl Comprehensive Cancer Network, 2019, doi.org/10.6004/jnccn.2018.0088 16. Clinical Expert Opinion. June 2019	
	The UK Mastocytosis Support Group	Any additional comments on the draft scope It should be noted that Masitinib (cited under "Related NICE recommendations and NICE Pathways") had trials only in indolent systemic mastocytosis, not in the advanced forms (ASM, SM-AHN and Mast Cell Leukaemia) for which Midostaurin has received marketing authorisation.	Comment noted. No change to the scope required.

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

Janssen