NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Contents:

The following documents are made available to consultees and commentators:

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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Leukaemia Care and UKMastocytosis

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Dr Steven Knapper – clinical expert, nominated by Novartis Pharmaceuticals

5. **Evidence Review Group critique of company comments on the ACD**

6. **Letter from company to NICE committee**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Midostaurin for treating advanced systemic mastocytosis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	We welcome the Committee's acknowledgement that midostaurin is more effective than current treatments, albeit that the evidence is uncertain due to the limited evidence base for advanced SM. Whilst the trial evidence for midostaurin is the largest available in the treatment of advanced SM, it is also reflective of that which is usually available for an ultra-rare and heterogeneous condition. We also welcome the Committee's acceptance that midostaurin meets NICE's criteria for a life-extending treatment at the end of life. We note that the current NICE STA process does not factor rarity or severity as a decision modifier as it does in the HST process. As highlighted by a recent report1 by the Blood Cancer Alliance (BCA), not all interventions for ultra-rare diseases are appraised via the HST programme (with the BCA citing this appraisal as an example). The impact of this differential routing is an inconsistency (compared to treatments with eligible populations of a similar size) in the size of the eligible patient population that might be considered small enough for appraisal via the HST process.1 Those ultra-orphan treatments that fail to fulfil the criteria for the HST route are therefore disadvantaged by the narrower perspective of the STA process. This disparity between programmes has been acknowledged in the ongoing NICE methods review consultation,2 with the Modifiers Task and Finish group recommending more flexibility in accepting uncertainty when considering treatments for rare diseases where it is recognised that generating evidence is complex and difficult. The outcome of this appraisal would now seem to depend on when Novartis proactively requested to make a submission for this indication, and when the invitation to participate (ITP) was issued. Depending on the outcome of the NICE methods review, midostaurin may have been recommended, had the ITP been delayed until after the NICE methods review has concluded. For context, advanced SM was excluded from the NICE review process initially as it was outside the revamped CDF 2016 mandate to appraise all new cancer drugs via NICE. Nevertheless, Novartis chose to pro-actively pursue reimbursement via NICE, notwithstanding the data limitations, in order to secure access for this patient population with high unmet need. Furthermore, this means that despite the availability of midostaurin, a licensed medicine, UK patients with advanced SM only have access to unlicensed treatments for which efficacy has not	Comments noted. Please see detailed responses to specific comments below. Following consultation, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.

	been demonstrated and where the existing evidence is weaker than the evidence provided by the trials of midostaurin as part of this appraisal. Novartis remain open to engaging with NHSE and NICE to enable access, given the very high unmet need in advanced SM. As explained in subsequent sections of this consultation response, we believe the assumption of a 3-year treatment benefit duration for midostaurin is highly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years. This view is supported by clinical experts we consulted. Keeping all of the committee's preferred assumptions, but assuming a 5-year treatment benefit duration for midostaurin results in a converged PSA ICER of [redacted] which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease.	
Novartis	Section 2.3 (Page 4): The annual cost of midostaurin based on the list price is reported as £146,359.33, but based on our calculations this should be £292,718.66. 56 x 25 mg capsules = £5,609.94. The dose of midostaurin is 100 mg twice daily thus 8 capsules are required per day. £5,609.94/7 *365.25 = annual cost of £292,718.66. Nb – there is an existing confidential patient access scheme in place for midostaurin	Comment noted. The annual cost of midostaurin based on the list price has been updated.
Novartis	Section 3.4 (Page 7) states "The Committee noted that most people in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years". This statement is potentially misleading based on the available data from the D2201 trial. In D2201, the median time to treatment discontinuation was 11.4 months and the mean duration of treatment was 23 months. The words 'most people' may inadvertently convey the wrong impression that a very large proportion of patients stopped treatment within 1 year, which is inaccurate. We request that this statement, which is mentioned twice in the document, is changed to: • "The Committee noted that most people just over half of people in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years".	Comments noted. The statement highlighted in the document is factually correct. This statement has been changed slightly to state "The committee noted that more than half of the people in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years"

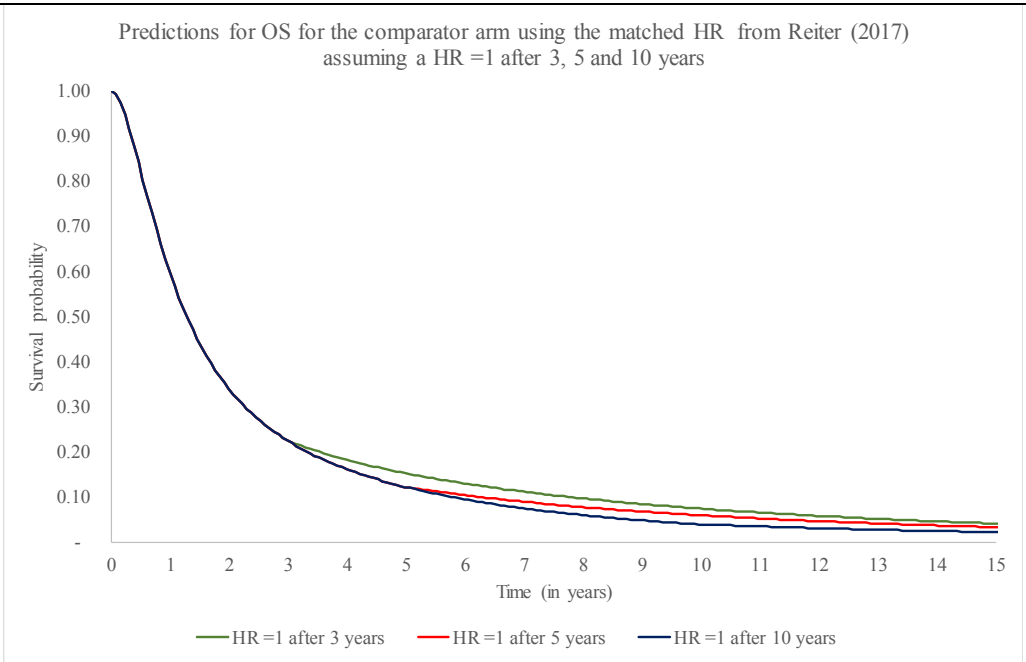
Novartis	Section 3.9 (Page 12) states "But they noted that disease response is often lost because of associated haematological malignancy instead of mastocytosis itself." This statement appears to apply to the AHN component of SM-AHN, rather than the whole advanced SM population. We ask that NICE checks this with clinical experts, and clarifies this statement accordingly.	Comment noted. The referenced statement has been changed in the final appraisal document to " ..disease response can be lost because of associated haematological malignancy instead of mastocytosis itself"
Novartis	Sections 3.4 and 3.9 The discussion on the Reiter et al. (2017)3 hazard ratio (HR) is potentially misleading without the added context that in the model the Reiter et al. (2017)3 hazard ratio (HR) is applied to the midostaurin arm to predict the comparator arm and that overall survival (OS) and Time to Treatment Discontinuation from D2201 are extrapolated directly with the D2201 trial data.	Comment noted. The current wording in the document is factually correct and therefore has not been changed.
Novartis	**Section 3.5 (Page 8):** discusses the committee's conclusion that the propensity score matched OS HR from the Reiter et al. (2017)[3] analysis should be used to inform the comparative effectiveness of midostaurin. Whilst acknowledging that matching approaches are often preferred, propensity score matched HR analysis has several limitations. About two thirds of patients initiating midostaurin in the pooled analysis of the D2201 and A2213 studies were subsequently excluded from this analysis (reducing the sample size from 115 to 42), increasing the level of uncertainty and potentially making the results less generalizable. Additionally, since matched analyses can only account for observed differences in the baseline characteristics, it is not clear if there were any unobserved differences in patient characteristics or other systematic differences between the midostaurin and registry data that may have affected the comparison. As explained in section 7 below, the cumulative impact of applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years compared to current clinical management, leads to implausible estimates for OS for the comparator arm as shown in Figure 1.	Comments noted. Section 3.5 noted the preferred choice of committee was the propensity score matched OS HR from the Reiter et al. (2017). The section also highlights that the committee acknowledged that this source is associated with uncertainty. Following consultation, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access

	In conclusion, the cumulative impact of applying propensity score matched OS HR from Reiter et al. (2017)3 AND assuming a HR of 1 after 3 years compared to current clinical management appears to be an overly pessimistic overall assessment of the evidence, given the acknowledged impact of midostaurin on quality of life and the limited ability to capture the quality of life benefits in the model due to data limitations.	arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.
Novartis	**Section 3.9 (Page 12)** states "*On balance, the committee concluded that it would consider a 3-year treatment benefit duration for midostaurin in its decision making, even though this was likely to be optimistic*" We consider a 3-year midostaurin benefit duration to be overly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years based on the following points: • As a point of clarification, the Reiter *et al. (*2017)[3] HR was applied to the midostaurin arm in order to predict the OS for the comparator arm. The predictions for the comparator arm, which represents what currently happens in clinical practice, were then validated with clinical experts. Table 1 and Figure 1 below present the predictions based on applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years, 5 years and 10 years. This shows that estimates for the comparator arm are more aligned with UK clinical practice when the HR is set to 1 after 10 years. However, we acknowledge the uncertainty and propose that at a minimum, the HR should be set to 1 at 5 years in order to generate plausible estimates for OS for the comparator arm. Feedback from clinical experts advised that only a small minority of patients would remain alive after 5 years using current clinical management, and therefore we believe that it is not appropriate to assume the treatment effect of midostaurin wanes before at least 5 years when looking at the predictions in Table 1 and Figure 1	Comments noted. Section 3.9 highlights that committee preferred to use a 3-year treatment benefit duration for midostaurin, acknowledging that this may be optimistic. The committee noted that most people did not continue to have midostaurin in the long term. Using committee's preferences described in section 3.11, and the updated commercial access arrangement, midostaurin was deemed cost-effective with ICER estimates below £50,000 per QALY gained for an end of life treatment and was recommended.

Table 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years

	HR = 1 after 3 years	HR = 1 after 5 years	HR = 1 after 10 years
Predicted OS of current clinical management at 5 years	**15.27%**	**12.24%**	**12.24%**
Predicted OS of current clinical management at 10 years	**7.37%**	**5.90%**	**3.91%**

Figure 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years



- The ERG had initially presented HR of 1 at 3 years as a scenario, to illustrate the impact on the ICERs as opposed to having a clinical justification.
- The Reiter *et al.* (2017) analysis data represents a median follow-up of over 6 years, thus providing evidence beyond 3 years. For context, Reiter *et al.* (2017) was updated with the latest data from the D2201 trial (final analysis of OS and safety data cut-off: 24th August 2017). Therefore, the data from D2201 and A2213 informing the HR for OS are based on cut-offs with median follow-up of [redacted] months ([redacted] years)[5] and 124 months (10.3 years),[6] respectively. These OS data already account for patients stopping treatment, which is therefore reflected in the extrapolations. The data from D2201 and A2213 suggest that patients treated with midostaurin are associated with a long duration of survival.

	Having considered that assuming a 3-year midostaurin benefit duration is overly pessimistic, we explored a scenario in which all of the committee's preferred assumptions are kept, except for assuming a 5-year treatment benefit duration for midostaurin. This scenario resulted in a converged PSA ICER of [redacted], which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease. Notwithstanding our view that assuming a 3-year midostaurin benefit duration is overly pessimistic, we also explored a scenario in which treatment costs are capped at 3 years and keeping all committee preferred assumptions the same. This analysis accounts for the fact that – if there 'truly' is a 3-year limit on the duration of treatment benefit – clinicians may stop treatment with midostaurin. Whilst we do not agree with what is tantamount to imposing a stopping rule at 3 years, not least because this is not in line with the marketing authorisation, this scenario resulted in a converged PSA ICER of [redacted]	
The UK Mastocytosis Support Group and Leukaemia Care	We are pleased that the committee have made the decision the end of life criteria applies to the whole group. This shows the impact that patient groups can have on the process and is an example of flexibility that needs to be applied due to uncertainty created by how rare this indication is. We are also pleased that both trials are being considered together given the rarity of the disease and the limited data available, and that the committee recognises there is unmet need in the advanced systemic mastocytosis community.	Comments noted.
The UK Mastocytosis Support Group and Leukaemia Care	Throughout the ACD, it is clear that too much uncertainty is a key barrier to a positive recommendation. However, as raised in our technical engagement response, the scarcity of evidence that is causing such uncertainty is due to the rarity of disease. We ask that the CDF be considered as an option to resolve these uncertainties. Additionally, this shows that the STA process is not appropriate for the appraisal of treatments for rare populations such as this that don't meet HST criteria. The HST process would have allowed for more uncertainty and so it is unfair that this treatment has been appraised through an inappropriate process.	Comments noted. As highlighted in the Appraisal Consultation Document (ACD) section 3.12, the committee was not aware of any planned future midostaurin or comparator studies that might resolve the key uncertainties. Also, it understood that data to inform comparative effectiveness could not be collected as part of the

		Cancer Drugs Fund. Therefore midostaurin is not an appropriate candidate for use in the Cancer Drugs Fund. Following consultation, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.
The UK Mastocytosis Support Group and Leukaemia Care	Point 3.5 highlights that the hazard ratios show midostaurin is more effective but is uncertain. However, this is a point of uncertainty that could be resolved by collection of data from patients who could access midostaurin through the CDF.	Comment noted. Please see previous response.

The UK Mastocytosis Support Group and Leukaemia Care	Point 3.9 states that the clinical expert said that, when it comes to progression whilst on treatment, this is often caused by an associated haematological neoplasm, rather than midostaurin itself. This is statement is only relevant to patients with the subtype of advanced systemic mastocytosis with an associated haematological neoplasm.	Comment noted. The referenced statement has been changed in the final appraisal document to " ..disease response can be lost because of associated haematological malignancy instead of mastocytosis itself".
The UK Mastocytosis Support Group and Leukaemia Care	Point 3.9 also states that 3 years of treatment benefit is likely to be pessimistic for those who remain on midostaurin. We have been in contact with four patients who were part of our survey, as outlined in our previous submission response. Those four patients have taken midostaurin for 17 months; 3 years and 4 months; five years and 3 months and more than 12 years respectively. This is, of course a small sample of patients, but shows it may be inappropriate to conclude that 3 years of treatment benefit is a reasonable assumption. In addition, there is registry data from the European Competence Network that we believe reinforces this. (Academic in confidence information removed). Given that MCL has the shortest life expectancy of the three conditions, and treatment with it as first line shows, (Academic in confidence information removed) we ask the committee to consider increasing the duration of treatment effect to at least five years.	Comments noted. Section 3.9 highlights that committee preferred to use a 3-year treatment benefit duration for midostaurin, acknowledging that this may be optimistic. The committee noted that most people did not continue to have midostaurin in the long term. Using committee's preferences described in section 3.11, and the updated commercial access arrangement, midostaurin was deemed cost-effective with ICER estimates below £50,000 per QALY gained for an end of life treatment and was recommended.
The UK Mastocytosis	Point 3.11 states that the cost-effectiveness estimates are higher than £100,000 per QALY, beyond the threshold considered in STA. This is based on prices agreed some time ago and this	Comment noted. Following consultation, the revised cost-

Support Group and Leukaemia Care	may have changed with recent negotiations. It is price that is in part hampering a positive recommendation and we urge NHSE and Novartis to come to an agreement. We believe that multi-indication pricing is hampering negotiations here because a price has already been agreed for midostaurin in another indication.	effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.
The UK Mastocytosis Support Group and Leukaemia Care	Point 3.11 also shows that this treatment would be cost effective if it had been appraised through the HST process at the previous agreed price without the most recent negotiations. Again, it is unfair that this treatment was appraised through the STA process when sufficient evidence cannot be obtained due to the rarity of the disease.	Comment noted.
The UK Mastocytosis Support Group and Leukaemia Care	Uncertainty about quality of life, as described in point 3.8, could also be resolved through collection of data. The company should be requested to collect this whilst the treatment is accessed via the CDF.	Comments noted. As highlighted in the Appraisal Consultation Document (ACD) section 3.12, the committee was not aware of any planned future midostaurin or comparator studies that might resolve the key uncertainties. Also, it understood that data to inform

		comparative effectiveness could not be collected as part of the Cancer Drugs Fund. Therefore midostaurin is not an appropriate candidate for use in the Cancer Drugs Fund. Using committee's preferences described in section 3.11, and the updated commercial access arrangement, midostaurin was deemed cost-effective with ICER estimates below £50,000 per QALY gained for an end of life treatment and was recommended.
The UK Mastocytosis Support Group and Leukaemia Care	We believe that the decision to assess this treatment through the STA process shows that the criteria for entering HST discriminates against rare cancer. There has never been a cancer treatment assessed through the HST process. The criteria, particularly the need to be a chronic and lifelong condition and only treated in specialist centres don't allow cancers to be appraised in HST, yet the patient populations being included in STA are becoming smaller and smaller, resulting in increased uncertainty and negative outcomes.	Comment noted.
The UK Mastocytosis Support Group and Leukaemia Care	This treatment is standard of care in all other countries (Academic in confidence information removed) and it is unfair that patients in the UK are disadvantaged in this way. We are aware of patients considering self-funding midostaurin in the UK as the treatment is the only option available, even taking clinical trials of newer medications into account as patients may not qualify for trials or the trials drugs may not be suitable. Patients with all subtypes of advanced systemic mastocytosis are in need of new treatments to both extend and improve quality of life, which this treatment can do.	Comment noted. Following consultation, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access

		arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.
The UK Mastocytosis Support Group and Leukaemia Care	We feel that in light of the new data that were presented at the European Competence Network on Mastocytosis meeting in late August (too late for submission before the September meeting) that the patient representatives should be invited to attend the second committee meeting to discuss further the question of duration of effect. Additional input would also be appropriate from the clinical experts who have also see this data.	Comment noted. Following consultation, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Clinical expert	Having participated in the appraisal meeting, I am happy that the appraisal consultation document provides a balanced reflection of the discussions around use of midostaurin for treatment of advanced systemic mastocytosis. At this point I merely wish to highlight that a very significant proportion of patients that are treated with midostaurin will be dosed at 50mg twice daily (rather than the initially recommended 100mg twice daily dose). In my clinical experience, the higher dose is regularly associated with gastrointestinal toxicity issues and many patients are reduced to the 50% dose fairly quickly, then spending the majority of their time on treatment at the lower dose (this is actually the approved dose in the other major indication of acute myeloid leukaemia). This dose reduction has applied to all 6-7 patients that I have personally treated; clinical efficacy is frequently seen at the lower dose. Given that the reduced dose also represents considerable potential cost savings, I feel that greater account could be taken of this in the cost modelling.	Comment noted. Following the first committee meeting, the revised cost-effectiveness results were below £50,000 per QALY gained for midostaurin using committee's preferred assumptions as detailed in section 3.11 in the final appraisal document, and the updated commercial access arrangement. Therefore, midostaurin is recommended, within its marketing authorisation, as an option for treating aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms or mast cell leukaemia (advanced systemic mastocytosis) in adults.

Comments received from commentators

No comments received

Comments received from members of the public

No comments received

NICE National Institute for Health and Care Excellence

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 27 November 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 27 November 2020 **email:** NICE DOCS

1	We welcome the Committee's acknowledgement that midostaurin is more effective than current treatments, albeit that the evidence is uncertain due to the limited evidence base for advanced SM. Whilst the trial evidence for midostaurin is the largest available in the treatment of advanced SM, it is also reflective of that which is usually available for an ultra-rare and heterogeneous condition. We also welcome the Committee's acceptance that midostaurin meets NICE's criteria for a life-extending treatment at the end of life. We note that the current NICE STA process does not factor rarity or severity as a decision modifier as it does in the HST process. As highlighted by a recent report[1] by the Blood Cancer Alliance (BCA), not all interventions for ultra-rare diseases are appraised via the HST programme (with the BCA citing this appraisal as an example). The impact of this differential routing is an inconsistency (compared to treatments with eligible populations of a similar size) in the size of the eligible patient population that might be considered small enough for appraisal via the HST process.[1] Those ultra-orphan treatments that fail to fulfil the criteria for the HST route are therefore disadvantaged by the narrower perspective of the STA process. This disparity between programmes has been acknowledged in the ongoing NICE methods review consultation,[2] with the Modifiers Task and Finish group recommending more flexibility in accepting uncertainty when considering treatments for rare diseases where it is recognised that generating evidence is complex and difficult. The outcome of this appraisal would now seem to depend on when Novartis proactively requested to make a submission for this indication, and when the invitation to participate (ITP) was issued. Depending on the outcome of the NICE methods review, midostaurin may have been recommended, had the ITP been delayed until after the NICE methods review has concluded. For context, advanced SM was excluded from the NICE review process initially as it was outside the revamped CDF 2016 mandate to appraise all new cancer drugs via NICE. Nevertheless, Novartis chose to pro-actively pursue reimbursement via NICE, notwithstanding the data limitations, in order to secure access for this patient population with high unmet need. Furthermore, this means that despite the availability of midostaurin, a licensed medicine, UK patients with advanced SM only have access to unlicensed treatments for which efficacy has not been demonstrated and where the existing evidence is

	weaker than the evidence provided by the trials of midostaurin as part of this appraisal. Novartis remain open to engaging with NHSE and NICE to enable access, given the very high unmet need in advanced SM. As explained in subsequent sections of this consultation response, we believe the assumption of a 3-year treatment benefit duration for midostaurin is highly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years. This view is supported by clinical experts we consulted. Keeping all of the committee's preferred assumptions, but assuming a 5-year treatment benefit duration for midostaurin results in a converged PSA ICER of [redacted] which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease.
2	**Section 2.3 (Page 4):** The annual cost of midostaurin based on the list price is reported as £146,359.33, but based on our calculations this should be **£292,718.66**. 56 x 25 mg capsules = £5,609.94. The dose of midostaurin is 100 mg twice daily thus 8 capsules are required per day. £5,609.94/7 *365.25 = annual cost of £292,718.66. Nb – there is an existing confidential patient access scheme in place for midostaurin
3	**Section 3.4 (Page 7)** states "*The Committee noted that **most people** in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years*". This statement is potentially misleading based on the available data from the D2201 trial. In D2201, the median time to treatment discontinuation was 11.4 months and the mean duration of treatment was 23 months. The words 'most people' may inadvertently convey the wrong impression that a very large proportion of patients stopped treatment within 1 year, which is inaccurate. We request that this statement, which is mentioned twice in the document, is changed to: • "*The Committee noted that **~~most people~~ just over half of people** in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years*".
4	**Section 3.9 (Page 12)** states **"***But they noted that disease response is often lost*

	because of associated haematological malignancy instead of mastocytosis itself." This statement appears to apply to the AHN component of SM-AHN, rather than the whole advanced SM population. We ask that NICE checks this with clinical experts, and clarifies this statement accordingly.
5	**Sections 3.4 and 3.9** The discussion on the Reiter et al. (2017)[3] hazard ratio (HR) is potentially misleading without the added context that in the model the Reiter et al. (2017)[3] hazard ratio (HR) is applied to the midostaurin arm to predict the comparator arm and that overall survival (OS) and Time to Treatment Discontinuation from D2201 are extrapolated directly with the D2201 trial data.
6	**Section 3.5 (Page 8):** discusses the committee's conclusion that the propensity score matched OS HR from the Reiter et al. (2017)[3] analysis should be used to inform the comparative effectiveness of midostaurin. Whilst acknowledging that matching approaches are often preferred, propensity score matched HR analysis has several limitations. About two thirds of patients initiating midostaurin in the pooled analysis of the D2201 and A2213 studies were subsequently excluded from this analysis (reducing the sample size from 115 to 42), increasing the level of uncertainty and potentially making the results less generalizable. Additionally, since matched analyses can only account for observed differences in the baseline characteristics, it is not clear if there were any unobserved differences in patient characteristics or other systematic differences between the midostaurin and registry data that may have affected the comparison. As explained in section 7 below, the cumulative impact of applying propensity score matched OS HR from *Reiter et al. (2017)[3]* **AND** assuming a HR of 1 after 3 years compared to current clinical management, leads to implausible estimates for OS for the comparator arm as shown in Figure 1. In conclusion, the cumulative impact of applying propensity score matched OS HR from *Reiter et al. (2017)[3]* **AND** assuming a HR of 1 after 3 years compared to current clinical management appears to be an overly pessimistic overall assessment of the evidence, given the acknowledged impact of midostaurin on quality of life and the limited ability to capture the quality of life benefits in the model due to data limitations.
7	**Section 3.9 (Page 12)** states "*On balance, the committee concluded that it would consider a 3-year treatment benefit duration for midostaurin in its decision making,*

even though this was likely to be optimistic"

We consider a 3-year midostaurin benefit duration to be overly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years based on the following points:

- As a point of clarification, the Reiter *et al. (*2017)[3] HR was applied to the midostaurin arm in order to predict the OS for the comparator arm. The predictions for the comparator arm, which represents what currently happens in clinical practice, were then validated with clinical experts. Table 1 and Figure 1 below present the predictions based on applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years, 5 years and 10 years. This shows that estimates for the comparator arm are more aligned with UK clinical practice when the HR is set to 1 after 10 years. However, we acknowledge the uncertainty and propose that at a minimum, the HR should be set to 1 at 5 years in order to generate plausible estimates for OS for the comparator arm. Feedback from clinical experts advised that only a small minority of patients would remain alive after 5 years using current clinical management, and therefore we believe that it is not appropriate to assume the treatment effect of midostaurin wanes before at least 5 years when looking at the predictions in Table 1 and Figure 1

Table 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years

	HR = 1 after 3 years	HR = 1 after 5 years	HR = 1 after 10 years
Predicted OS of current clinical management at 5 years	**15.27%**	**12.24%**	**12.24%**
Predicted OS of current clinical management at 10 years	**7.37%**	**5.90%**	**3.91%**

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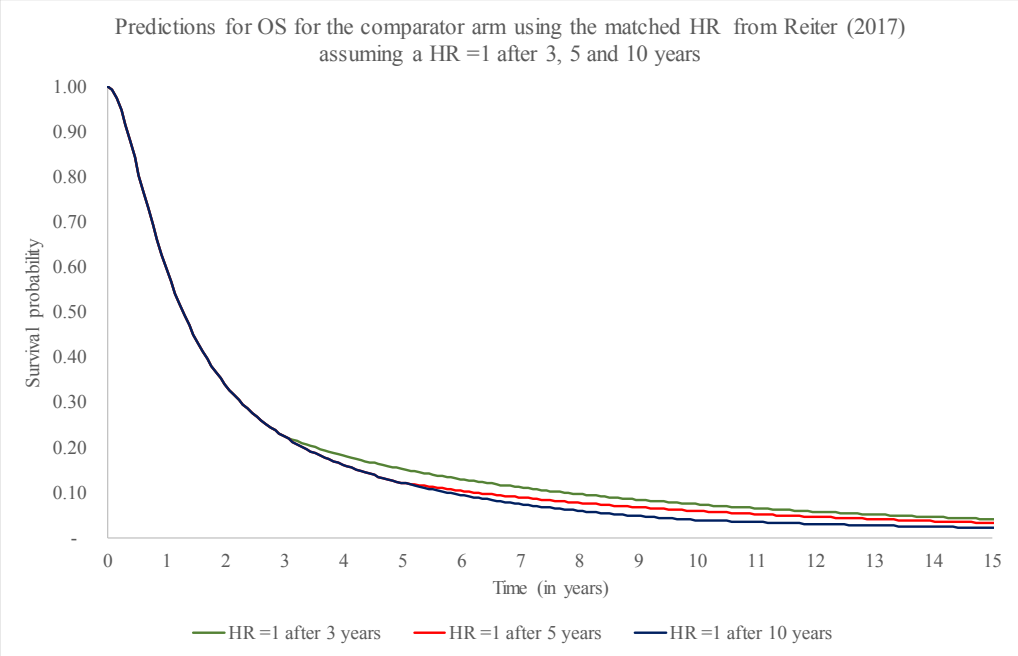
Figure 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years



- The ERG had initially presented HR of 1 at 3 years as a scenario, to illustrate the impact on the ICERs as opposed to having a clinical justification.

- The Reiter *et al.* (2017) analysis data represents a median follow-up of over 6 years, thus providing evidence beyond 3 years. For context, Reiter *et al.* (2017) was updated with the latest data from the D2201 trial (final analysis of OS and safety data cut-off: 24th August 2017). Therefore, the data from D2201 and A2213 informing the HR for OS are based on cut-offs with median follow-up of [redacted] months ([redacted] years)[5] and 124 months (10.3 years),[6] respectively. These OS data already account for patients stopping treatment, which is therefore reflected in the extrapolations. The data from D2201 and A2213 suggest that patients treated with midostaurin are associated with a long duration of survival.

Having considered that assuming a 3-year midostaurin benefit duration is overly pessimistic, we explored a scenario in which all of the committee's preferred assumptions are kept, except for assuming a 5-year treatment benefit duration for

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	midostaurin. This scenario resulted in a converged PSA ICER of [redacted], which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease. Notwithstanding our view that assuming a 3-year midostaurin benefit duration is overly pessimistic, we also explored a scenario in which treatment costs are capped at 3 years and keeping all committee preferred assumptions the same. This analysis accounts for the fact that – if there 'truly' is a 3-year limit on the duration of treatment benefit – clinicians may stop treatment with midostaurin. Whilst we do not agree with what is tantamount to imposing a stopping rule at 3 years, not least because this is not in line with the marketing authorisation, this scenario resulted in a converged PSA ICER of [redacted]

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The UK Mastocytosis Support Group and Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are pleased that the committee have made the decision the end of life criteria applies to the whole group. This shows the impact that patient groups can have on the process and is an example of flexibility that needs to be applied due to uncertainty created by how rare this indication is. We are also pleased that both trials are being considered together given the rarity of the disease and the limited data available, and that the committee recognises there is unmet need in the advanced systemic mastocytosis community.
2	Throughout the ACD, it is clear that too much uncertainty is a key barrier to a positive recommendation. However, as raised in our technical engagement response, the scarcity of evidence that is causing such uncertainty is due to the rarity of disease. We ask that the CDF be considered as an option to resolve these uncertainties. Additionally, this shows that the STA process is not appropriate for the appraisal of treatments for rare populations such as this that don't meet HST criteria. The HST process would have allowed for more uncertainty and so it is unfair that this treatment has been appraised through an inappropriate process.
6	Point 3.5 highlights that the hazard ratios show midostaurin is more effective but is uncertain. However, this is a point of uncertainty that could be resolved by collection of data from patients who could access midostaurin through the CDF.
7	Point 3.9 states that the clinical expert said that, when it comes to progression whilst on treatment, this is often caused by an associated haematological neoplasm, rather than midostaurin itself. This is statement is only relevant to patients with the subtype of advanced systemic mastocytosis with an associated haematological neoplasm.
8	Point 3.9 also states that 3 years of treatment benefit is likely to be pessimistic for those who remain on midostaurin. We have been in contact with four patients who were part of our survey, as outlined in our previous submission response. Those four patients have taken midostaurin for 17 months; 3 years and 4 months; five years and 3 months and more than 12 years respectively. This is, of course a small sample of patients, but shows it may be inappropriate to conclude that 3 years of treatment benefit is a reasonable assumption. In addition, there is registry data from the European Competence Network that we believe reinforces this. (Academic in confidence information removed). Given that MCL has the shortest life expectancy of the three conditions, and treatment with it as first line shows, (Academic in confidence information removed) we ask the committee to consider increasing the duration of treatment effect to at least five years.
9	Point 3.11 states that the cost-effectiveness estimates are higher than £100,000 per QALY, beyond the threshold considered in STA. This is based on prices agreed some time ago and this may have changed with recent negotiations. It is price that is in part hampering a positive recommendation and we urge NHSE and Novartis to come to an agreement. We believe that multi-indication pricing is hampering negotiations here because a price has already been agreed for midostaurin in another indication.
10	Point 3.11 also shows that this treatment would be cost effective if it had been appraised through the HST process at the previous agreed price without the most recent negotiations. Again, it is unfair that this treatment was appraised through the STA process when sufficient evidence cannot be obtained due to the rarity of the disease.
11	Uncertainty about quality of life, as described in point 3.8, could also be resolved through collection of data. The company should be requested to collect this whilst the treatment is accessed via the CDF.
12	We believe that the decision to assess this treatment through the STA process shows that the criteria for entering HST discriminates against rare cancer. There has never been a cancer treatment assessed through the HST process. The criteria, particularly the need to be a chronic and lifelong condition and only treated in specialist centres don't allow cancers to be appraised in HST, yet the patient populations being included in STA are becoming smaller and smaller, resulting in increased uncertainty and negative outcomes.
13	This treatment is standard of care in all other countries (Academic in confidence information

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	removed) and it is unfair that patients in the UK are disadvantaged in this way. We are aware of patients considering self-funding midostaurin in the UK as the treatment is the only option available, even taking clinical trials of newer medications into account as patients may not qualify for trials or the trials drugs may not be suitable. Patients with all subtypes of advanced systemic mastocytosis are in need of new treatments to both extend and improve quality of life, which this treatment can do.
14	We feel that in light of the new data that were presented at the European Competence Network on Mastocytosis meeting in late August (too late for submission before the September meeting) that the patient representatives should be invited to attend the second committee meeting to discuss further the question of duration of effect. Additional input would also be appropriate from the clinical experts who have also see this data.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cardiff University / University Hospital of Wales (nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil to disclose
Name of commentator person completing form:	Dr Steven Knapper

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Having participated in the appraisal meeting, I am happy that the appraisal consultation document provides a balanced reflection of the discussions around use of midostaurin for treatment of advanced systemic mastocytosis. At this point I merely wish to highlight that a very significant proportion of patients that are treated with midostaurin will be dosed at 50mg twice daily (rather than the initially recommended 100mg twice daily dose). In my clinical experience, the higher dose is regularly associated with gastrointestinal toxicity issues and many patients are reduced to the 50% dose fairly quickly, then spending the majority of their time on treatment at the lower dose (this is actually the approved dose in the other major indication of acute myeloid leukaemia). This dose reduction has applied to all 6-7 patients that I have personally treated; clinical efficacy is frequently seen at the lower dose. Given that the reduced dose also represents considerable potential cost savings, I feel that greater account could be taken of this in the cost modelling.
2	
3	
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	We welcome the Committee's acknowledgement that midostaurin is more effective than current treatments, albeit that the evidence is uncertain due to the limited evidence base for advanced SM. Whilst the trial evidence for midostaurin is the largest available in the treatment of advanced SM, it is also reflective of that which is usually available for an ultra-rare and heterogeneous condition. We also welcome the Committee's acceptance that midostaurin meets NICE's criteria for a life-extending treatment at the end of life. We note that the current NICE STA process does not factor rarity or severity as a decision modifier as it does in the HST process. As highlighted by a recent report[1] by the Blood Cancer Alliance (BCA), not all interventions for ultra-rare diseases are appraised via the HST programme (with the BCA citing this appraisal as an example). The impact of this differential routing is an inconsistency (compared to treatments with eligible populations of a similar size) in the size of the eligible patient population that might be considered small enough for appraisal via the HST process.[1] Those ultra-orphan treatments that fail to fulfil the criteria for the HST route are therefore disadvantaged by the narrower perspective of the STA process. This disparity between programmes has been acknowledged in the ongoing NICE methods review consultation,[2] with the Modifiers Task and Finish group recommending more flexibility in accepting uncertainty when considering treatments for rare diseases where it is recognised that generating evidence is complex and difficult. The outcome of this appraisal would now seem to depend on when Novartis proactively requested to make a submission for this indication, and when the invitation to participate (ITP) was issued. Depending on the outcome of the NICE methods review, midostaurin may have been recommended, had the ITP been delayed until after the NICE methods review has concluded. For context, advanced SM was excluded from the NICE review process initially as it was outside the revamped CDF 2016 mandate to appraise all new cancer drugs via NICE. Nevertheless, Novartis chose to pro-actively pursue reimbursement via NICE, notwithstanding the data limitations, in order to secure access for this patient population with high unmet need. Furthermore, this means that despite the availability of midostaurin, a licensed medicine, UK patients with advanced SM only have access to unlicensed treatments for which efficacy has not been demonstrated and where the existing evidence is

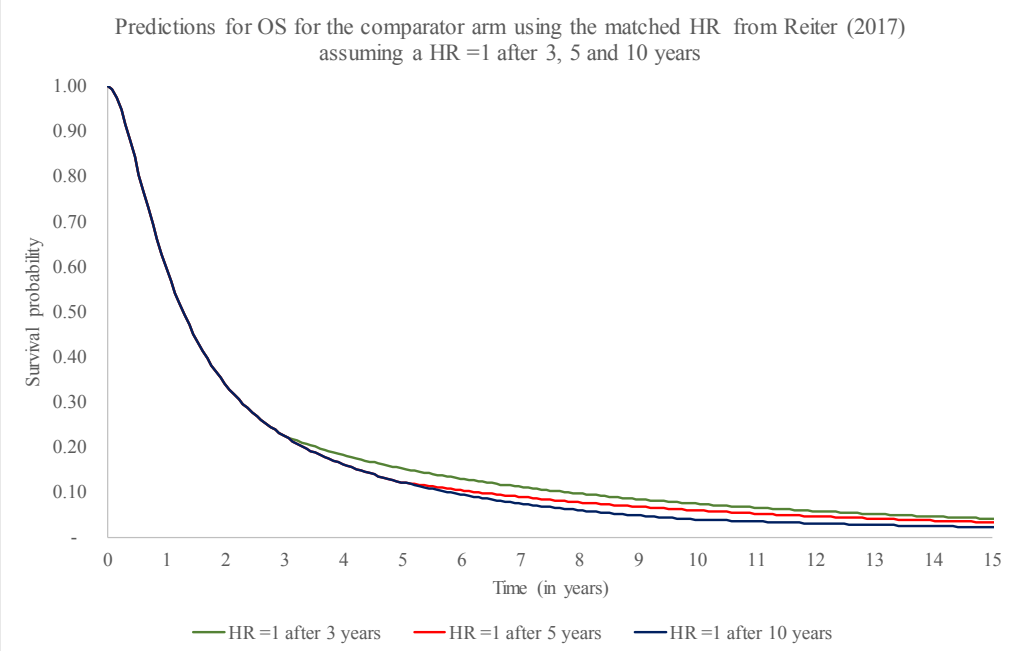
	weaker than the evidence provided by the trials of midostaurin as part of this appraisal. Novartis remain open to engaging with NHSE and NICE to enable access, given the very high unmet need in advanced SM. As explained in subsequent sections of this consultation response, we believe the assumption of a 3-year treatment benefit duration for midostaurin is highly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years. This view is supported by clinical experts we consulted. Keeping all of the committee's preferred assumptions, but assuming a 5-year treatment benefit duration for midostaurin results in a converged PSA ICER of [redacted], which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease.
ERG response	No comment
2	**Section 2.3 (Page 4):** The annual cost of midostaurin based on the list price is reported as £146,359.33, but based on our calculations this should be **£292,718.66**. 56 x 25 mg capsules = £5,609.94. The dose of midostaurin is 100 mg twice daily thus 8 capsules are required per day. £5,609.94/7 *365.25 = annual cost of £292,718.66. Nb – there is an existing confidential patient access scheme in place for midostaurin
ERG response	No comment
3	**Section 3.4 (Page 7)** states "*The Committee noted that **most people** in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years*". This statement is potentially misleading based on the available data from the D2201 trial. In D2201, the median time to treatment discontinuation was 11.4 months and the mean duration of treatment was 23 months. The words 'most people' may inadvertently convey the wrong impression that a very large proportion of patients stopped treatment within 1 year, which is inaccurate. We request that this statement, which is mentioned twice in the document, is changed to: • "*The Committee noted that **~~most people~~ just over half of people** in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still*

	having treatment at 3 years".
ERG response	No comment
4	**Section 3.9 (Page 12)** states **"***But they noted that disease response is often lost because of associated haematological malignancy instead of mastocytosis itself*." This statement appears to apply to the AHN component of SM-AHN, rather than the whole advanced SM population. We ask that NICE checks this with clinical experts, and clarifies this statement accordingly.
ERG response	No comment
5	**Sections 3.4 and 3.9** The discussion on the Reiter et al. (2017)[3] hazard ratio (HR) is potentially misleading without the added context that in the model the Reiter et al. (2017)[3] hazard ratio (HR) is applied to the midostaurin arm to predict the comparator arm and that overall survival (OS) and Time to Treatment Discontinuation from D2201 are extrapolated directly with the D2201 trial data.
ERG response	No comment
6	**Section 3.5 (Page 8):** discusses the committee's conclusion that the propensity score matched OS HR from the Reiter et al. (2017)[3] analysis should be used to inform the comparative effectiveness of midostaurin. Whilst acknowledging that matching approaches are often preferred, propensity score matched HR analysis has several limitations. About two thirds of patients initiating midostaurin in the pooled analysis of the D2201 and A2213 studies were subsequently excluded from this analysis (reducing the sample size from 115 to 42), increasing the level of uncertainty and potentially making the results less generalizable. Additionally, since matched analyses can only account for observed differences in the baseline characteristics, it is not clear if there were any unobserved differences in patient characteristics or other systematic differences between the midostaurin and registry data that may have affected the comparison. As explained in section 7 below, the cumulative impact of applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years compared to current clinical management, leads to implausible estimates for OS for the comparator arm as shown in Figure 1.

	In conclusion, the cumulative impact of applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years compared to current clinical management appears to be an overly pessimistic overall assessment of the evidence, given the acknowledged impact of midostaurin on quality of life and the limited ability to capture the quality of life benefits in the model due to data limitations.
ERG response	No comment
7	**Section 3.9 (Page 12)** states "*On balance, the committee concluded that it would consider a 3-year treatment benefit duration for midostaurin in its decision making, even though this was likely to be optimistic*" We consider a 3-year midostaurin benefit duration to be overly pessimistic and would propose at least 5 years treatment benefit duration for midostaurin and possibly 10 years based on the following points: • As a point of clarification, the Reiter *et al. (*2017)[3] HR was applied to the midostaurin arm in order to predict the OS for the comparator arm. The predictions for the comparator arm, which represents what currently happens in clinical practice, were then validated with clinical experts. Table 1 and Figure 1 below present the predictions based on applying propensity score matched OS HR from *Reiter et al. (2017)*[3] **AND** assuming a HR of 1 after 3 years, 5 years and 10 years. This shows that estimates for the comparator arm are more aligned with UK clinical practice when the HR is set to 1 after 10 years. However, we acknowledge the uncertainty and propose that at a minimum, the HR should be set to 1 at 5 years in order to generate plausible estimates for OS for the comparator arm. Feedback from clinical experts advised that only a small minority of patients would remain alive after 5 years using current clinical management, and therefore we believe that it is not appropriate to assume the treatment effect of midostaurin wanes before at least 5 years when looking at the predictions in Table 1 and Figure 1 **Table 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years** | | HR = 1 after 3 | HR = 1 after 5 | HR = 1 after 10 |

	years	years	years
Predicted OS of current clinical management at 5 years	**15.27%**	**12.24%**	**12.24%**
Predicted OS of current clinical management at 10 years	**7.37%**	**5.90%**	**3.91%**

Figure 1 – Predictions for OS for current clinical management based on propensity score matched OS HR from *Reiter et al. (2017)*[3] AND assuming a HR of 1 after 3 years, 5 years and 10 years



- The ERG had initially presented HR of 1 at 3 years as a scenario, to illustrate the impact on the ICERs as opposed to having a clinical justification.

- The Reiter *et al.* (2017) analysis data represents a median follow-up of over 6 years, thus providing evidence beyond 3 years. For context, Reiter *et al.* (2017) was updated with the latest data from the D2201 trial (final analysis of OS and safety data cut-off: 24th August 2017). Therefore, the data from D2201 and A2213

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	informing the HR for OS are based on cut-offs with median follow-up of ** months (**** years)[5] and 124 months (10.3 years),[6] respectively. These OS data already account for patients stopping treatment, which is therefore reflected in the extrapolations. The data from D2201 and A2213 suggest that patients treated with midostaurin are associated with a long duration of survival. Having considered that assuming a 3-year midostaurin benefit duration is overly pessimistic, we explored a scenario in which all of the committee's preferred assumptions are kept, except for assuming a 5-year treatment benefit duration for midostaurin. This scenario resulted in a converged PSA ICER of **********, which is within the margins of cost-effectiveness at a £50,000 per QALY willingness to pay (WTP) threshold, given the rarity and severity of the disease. Notwithstanding our view that assuming a 3-year midostaurin benefit duration is overly pessimistic, we also explored a scenario in which treatment costs are capped at 3 years and keeping all committee preferred assumptions the same. This analysis accounts for the fact that – if there 'truly' is a 3-year limit on the duration of treatment benefit – clinicians may stop treatment with midostaurin. Whilst we do not agree with what is tantamount to imposing a stopping rule at 3 years, not least because this is not in line with the marketing authorisation, this scenario resulted in a converged PSA ICER of **********
ERG response	As there is limited evidence on the duration of treatment effect for midostaurin after treatment has stopped, any analysis of waning of effect is speculative. The approach used by the company and the ERG to model a duration of midostaurin treatment effect is very simplistic and assumes that patients treated with midostaurin receive no benefit at 3, 5 and 10 years, regardless of when (or if) they stop treatment. In a partitioned survival model, it is difficult to model treatment effect from the point treatment stops. The ICER per QALY gained associated with a 3-year duration of treatment effect (implemented in the company model that was used for decision making in AC1) is not an ICER for a 3-year treatment effect after stopping treatment but is an ICER for a 3-year treatment effect from the start of treatment. This ICER is higher than the ICER that would be generated if treatment effect was modelled to last for 3 years beyond the point that treatment with midostaurin stopped.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Professor Stephen O'Brien
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1st July 2021

Dear Professor O'Brien,

Midostaurin for treating advanced systemic mastocytosis (advanced SM) [ID1573]

In advance of Committee meeting 2 for the appraisal of midostaurin (ID1573: provisionally scheduled for 13th July 2021), there have been a number of recent developments which we would like to bring to your attention. We ask that this letter and its contents to be considered alongside our response to the ACD (uploaded to NICE Docs on 26th November 2020).

As part of our response to the ACD, we provided an analysis which presented the Committee-preferred assumptions, with the single exception of the duration of treatment benefit: whilst the Committee-preferred assumption was 3 years, we presented a case for 5 years. The Novartis-preferred assumption, combined with all other Committee-preferred assumptions, led to an ICER of [redacted]. This was based on the output of a converged probabilistic sensitivity analysis, and used a discount which was specific to advanced SM [redacted].

The updates since our response to the ACD can be summarised as follows:

- [redacted]
- [redacted] based on the Committee-preferred assumptions outlined in the ACD. This equates to an ICER of [redacted] based on the latest version of the economic model sent to NICE. (*Nb - the presence of a confidential PAS for azacitidine means that the actual discount required to be cost-effective may actually be lower than* [redacted]
- As described above, our response to the ACD made a case for changing one of the Committee-preferred assumptions: a treatment benefit of 5 years duration, rather than 3 years. The 5-year treatment benefit assumption is supported by the clinical community and patient groups. If accepted by the Committee, it would reduce the discount required to be cost-effective to [redacted] (*see Table 1 below*).

Table 1

	Committee's Preferred Assumptions	Novartis Revised Assumptions
Assumptions	• Using the Reiter et al. propensity score matched overall survival hazard ratio • Using a single progression-free survival health state, with a single utility value from the company's revised analysis • Assuming the treatment benefit of midostaurin lasts for **3 years**, after which its progression and survival rates becomes equal to the comparator	Same as committee's assumptions, except: • Assuming the treatment benefit of midostaurin lasts for **5 years**, after which its progression and survival rates becomes equal to the comparator
Discount		
ICER		

- Novartis' intention is to avoid any further delays to patient access, based on the significant unmet need in advanced SM. Although to be confirmed, NICE has also suggested that a positive recommendation could be achieved without a further Committee Meeting, . An adjustment in the assumed duration of treatment benefit could only be agreed at a Committee Meeting: this would not only cause delay, but would also take up valuable time at these meetings.
- Table 2 below shows the ICERS at a discount of

Table 2

	Committee's Preferred Assumptions	Novartis Revised Assumptions
Commercial Offer discount		
ICER		

Conclusion

When assessing the cost-effectiveness of a medicine for a very rare disease via the STA route, it is a significant challenge There is a high degree of uncertainty that comes with a paucity of data in a very rare condition, and the level of discount required to address this is very significant. Nevertheless,

This can be summarised as follows:

1. The meets the cost-effective price (*table 2*) (depending on assumed duration of treatment benefit) over a 5 year period.
2. Our proposal helps to meet a significant unmet need in the NHS. Midostaurin, an oral capsule, is the only licensed treatment for advanced SM, which is a rare condition and treated at only three provider centres across England.

3. The offer comes with an implementation approach that is manageable for the NHS in terms of administrative burden.
4. [redacted]

[redacted] Our hope is that this appraisal can then proceed to a positive FAD without the need for a second Committee Meeting. Should this appraisal proceed to committee meeting 2, we would like it stated on the public record of proceedings that Novartis offered a cost-effective price, based on the committee's original preferred assumptions.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further

Yours sincerely,

[redacted]

Head of Health Economics and Policy
Phone: [redacted]
Email: [redacted]

[redacted]