**APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR MOGAMULIZUMAB FOR PREVIOUSLY TREATED MYCOSIS FUNGOIDES AND SÉZARY SYNDROME**

**EXECUTIVE SUMMARY**

Mycosis fungoides (MF) and Sézary syndrome (SS) are two subtypes of cutaneous T-cell lymphoma (CTCL). CTCL is a rare blood cancer that is serious, debilitating, and potentially life-threatening. NHS England’s Hospital Episodes Statistics data, over 10 years shows that adults with advanced disease in CTCL have significantly poorer outcomes compared to those presenting at an early stage. Today, these patients have a limited number of therapeutic options available to them.

As a rare disease, there is only a small patient population. This fact goes hand in hand with significant challenges to gather data in a scientifically robust way and hence address all possible questions and uncertainty. Despite such challenges in patient numbers and complexity of their previous interventions, the pivotal clinical trial investigating mogamulizumab, the MAVORIC study, is the largest clinical trial ever conducted in any subgroup of patients with CTCL.  MAVORIC is the first Phase III trial to include patients with Sézary syndrome. This unique study provides outcomes for the largest number of Sézary syndrome patients ever to be included in a randomised controlled clinical trial. The trial was conducted at 61 sites in 11 countries, of which 16 were in Europe including 3 in England.

Due to the rare disease nature of the population recruited into the MAVORIC study they had already been treated with and had become refractory to all known treatment options available in CTCL. Thus, to ethically recruit into such a clinical trial for a rare disease, the European Medicines Agency approved the study design for a totally new comparator agent to be used.  With all the quantity of clinical trial and real world data provided for the disease area and medicine,  mogamulizumab has demonstrated improved efficacy in all key areas of disease management, including progression free survival, overall survival, time to next treatment and health-related quality of life in affected patients.   Against this background Kyowa Kirin is surprised by the conclusion of the Committee as set out in the FAD and believes this is incorrect.

Kyowa Kirin’s appeal is based on the following grounds:

**Ground 1**

* The Committee’s decision that allogenic stem cell transplant should not be included in the economic modelling for mogamulizumab because aSCT had not been permitted in the MAVORIC trial is unfair
* The Committee’s conclusion that the IPCW-adjusted curve was not clinically plausible for the average person in the modelled population with severe disease is unexplained
* The Committee’s decision not to include carer utilities in the economic model is based on conclusions which are inconsistent with NICE’s Methods Guide and inadequately explained
* The Committee’s conclusion that mogamulizumab is not a life-extending treatment at the end of life relies on evidence which has not been disclosed and is therefore unfair
* The Committee’s conclusions regarding the ICER threshold for this appraisal do not take into account the factors identified in NICE’s Methods Guide
* The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal do not assess uncertainty in accordance with NICE’s Methods Guide
* The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal lack transparency
* The Committee’s conclusions regarding the most plausible ICER for this appraisal lack transparency
* The Committee’s statement that the relevant benefits associated with mogamulizumab could be adequately captured in the model disregards its own conclusions, is inconsistent with NICE’s procedures and lacks transparency

**Ground 2**

* The Committee’s conclusion that data from the Hospital Episodes Statistics (HES) database was not adequately matched to the data from MAVORIC is incorrect and unreasonable
* The Committee’s reliance on the TSE method to produce OS estimates for survival in the standard care arm of MAVORIC is inconsistent with the available evidence
* The Committee’s conclusions regarding the disease-modifying effects of mogamulizumab disregard expert evidence and misinterpret the evidence of one patient expert and are therefore unreasonable
* The Committee’s conclusion that it was not convinced that mogamulizumab provides an OS benefit is unreasonable in light of the evidence available
* The Committee’s conclusion that mogamulizumab is not considered to be a life-extending treatment at the end of life relies on incorrect and irrelevant data and is therefore unreasonable

**INTRODUCTION**

We provide below background information in relation to mycosis fungoides and Sézary syndrome and regarding mogamulizumab, in order to assist the Appeal Panel. This summary does not however replace the more detailed information provided by Kyowa Kirin in its original submission for the purposes of this appraisal.

**Mycosis fungoides and Sézary syndrome**

Cutaneous T-cell lymphoma (CTCL) is a rare, serious, debilitating and potentially life-threatening form of cancer (non-Hodgkin’s lymphoma) with profound skin manifestations, including erythroderma, scaly patches and skin tumours, that severely impact the quality of life of people living with the disease when it is poorly controlled. CTCL can also affect the blood, lymph nodes and internal organs.

Living with a diagnosis of mycosis fungoides or Sézary syndrome, two subtypes of CTCL is challenging, both from a symptoms’ management and psycho-social perspective.

Both sub-diseases are rare, falling within the definition of orphan diseases. A U.K. National Cancer Information Network audit of newly diagnosed cases of CTCL from 2009 to 2013 identified 42 cases of Sézary syndrome and 920 cases of mycosis fungoides in England, out of which, based on NICE TA577, 60% (552 of mycosis fungoides patients) is estimated to be advanced over this 5-year period, leading to a total of 119 patients per year.

While mycosis fungoides may be relatively indolent in its early stages, for patients who progress, median survival is only around 1.4-6 years from diagnosis of advanced disease depending on disease stage. Sézary syndrome is more aggressive with recorded median survival rates of less than 4 years from diagnosis.

Around 30% of patients with mycosis fungoides develop advanced disease, associated with generalised [erythroderma](https://en.wikipedia.org/wiki/Erythroderma), with severe [pruritus](https://en.wikipedia.org/wiki/Itch) and scaling, tumours, ulceration, lymphadenopathy and systemic involvement,.

Sézary syndrome is a more aggressive, leukaemic form of CTCL characterised by the presence of malignant lymphocytes, known as Sézary cells, in the peripheral blood. Affected patients have widespread erythroderma and may also have lymphadenopathy and thickened, scaly and fissured skin, affecting the skin generally, but particularly the palms and soles. Other signs and symptoms may include intense pruritis, fever; weight loss; hair loss; outward turning of the eyelids (ectropion); malformations of the nails; and hepatosplenomegaly.

The symptoms associated with both conditions are highly disabling and exert a major negative impact on health-related quality of life. The effects of disease and its management impose a substantial burden on both patients and their carers.

Due to the rarity of the conditions, limited treatment options and the heterogeneous nature of CTCL, treatment pathways are not well defined. Data obtained from the National Health Service’s own Hospital Episodes Statistics (HES) database, which includes all patients with mycosis fungoides and Sézary syndrome treated in secondary care over a 10-year period, demonstrates the lack of standard of care currently used in secondary care in the NHS. For patients with advanced disease (including all Sézary syndrome patients), treatment consists of topical therapies followed by first line systemic treatments, such as bexarotene, interferon, methotrexate, extracorporeal photophoresis, electron beam radiotherapy or chemotherapy. For patients who progress on or following first line systemic treatment, there are little data on the effects of the limited treatment options. However, analysis of the HES data shows poor survival (1.5 years) for patients receiving second line treatment onwards. Brentuximab vedotin is authorised for advanced stage patients who are CD-30 positive (around 23% of mycosis fungoides patients, but no patients with Sézary syndrome) and clinically eligible. Only very few effective treatment options achieve good disease control and are well-tolerated by adults with MF and SS. The only potentially curative treatment is allogenic stem cell transplant (aSCT), which may be offered to certain patients. Approximately 14% of patients in England will proceed to receive aSCT in all treatment lines, with around 5.2 % of patients receiving aSCT after second line systemic therapy.

**Mogamulizumab (Poteligeo)**

Mogamulizumab is a novel immune-oncology medicinal product which has orphan designation in the EU. It has demonstrated improved efficacy in all key areas of disease management, including progression free survival, overall survival, time to next treatment and health-related quality of life, compared to an active comparator in both adults with advanced mycosis fungoides and Sézary syndrome who are clinically ineligible for or refractory to brentuximab vedotin. Mogamulizumab was granted Promising Innovative Medicine (PIM) designation by the MHRA in March 2018 for the treatment of advanced refractory mycosis fungoides and Sézary syndrome.

MAVORIC, the pivotal clinical trial investigating mogamulizumab, is the largest clinical trial ever conducted in any subgroup of patients with CTCL. It is the first phase III trial to include patients with Sézary syndrome and provides outcomes for the largest number of Sézary syndrome patients ever to be included in a randomised controlled clinical trial. The trial was conducted at 61 sites in 11 countries, of which 16 were in Europe including 3 in England. Participants in the MAVORIC trial had failed a median of three prior systemic therapies. The choice the comparator, vorinostat, was, in part, driven by ethical considerations i.e., not exposing participants to a prior therapy which had already failed.

For the purposes of this appraisal, Kyowa Kirin proposed use of the product for a subset of patients eligible for treatment in accordance with the marketing authorisation, namely for the treatment of mycosis fungoides or Sézary syndrome after at least one previous systemic treatment for patients with advanced disease that has progressed with brentuximab vedotin or if such treatment is not appropriate.

**PROCEDURAL HISTORY OF THE APPRAISAL**

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| **Date** | **Event** |
| 5 December 2017 | Referral to NICE |
| 22 November 2018 | Mogamulizumab approved by the European Commission for the treatment of adult patients with mycosis fungoides or Sézary syndrome who have received at least 1 prior systemic therapy. |
| October 2019 | Final scope for appraisal |
| January 2020 | Kyowa Kirin submission to NICE |
| 18 March 2020 | Report by Evidence Review Group (ERG), Kleijnen Systematic Reviews Ltd |
| 7 July 2020 | Original date for first meeting of Appraisal Committee as originally allocated to Committee C |
| 8 July 2020 | First meeting of Appraisal Committee following reallocation to Committee D |
| 30 July 2020 | Appraisal Consultation Document issued  “Mogamulizumab is not recommended, within its marketing authorisation, for treating mycosis fungoides or Sézary syndrome in adults who have had at least 1 previous systemic treatment” |
| 19 August 2020 | Kyowa Kirin and other consultees and commentators submit responses to consultation on ACD. |
| 13 January 2021 | Second meeting of the Appraisal Committee |
| 25 February 2021 | Final Appraisal Document issued  Recommendations unchanged from those in ACD |
| 18 March 2021 | Deadline for submission of appeal |

**GROUNDS OF APPEAL**

1. **GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS**
   1. **The Committee’s decision that allogenic stem cell transplant should not be included in the economic modelling for mogamulizumab because aSCT had not been permitted in the MAVORIC trial is unfair:**

The conclusion of the Appraisal Committee at paragraph 3.7 of the FAD, that allogenic stem cell transplant (aSCT) should not be included in the economic modelling for mogamulizumab is unfair including for the following reasons.

* The use of aSCT for a limited number of patients represents standard care within the NHS in England;
* The Committee’s concerns were addressed in a scenario analysis submitted in response to the ACD, which has not been taken into account; and
* No reason has been provided for diverging from the approach followed in TA577, which considered brentuximab vedotin, in which rates of aSCT higher than those seen in the pivotal clinical trial were accepted for the purposes of guidance.

The Committee rejected the incorporation of aSCT in the economic model for mogamulizumab on the basis that, aSCT was not permitted in the MAVORIC trial after current treatment and “*to avoid double-counting survival benefit in MAVORIC and to reduce potential bias*”. The issue of double-counting is said to arise in circumstances where patients eligible for potentially curative aSCT are likely to be those who respond well to treatment and therefore have a longer overall survival, as reflected in the trial data and already incorporated in the economic modelling.

1. Kyowa Kirin does not believe exclusion of aSCT from the economic model is fair in circumstances where there is a clear bias arising from the exclusion of aSCT which forms part of NHS standard care in England. A key benefit of mogamulizumab treatment is the possibility that this may be used as a bridge to aSCT, the only curative treatment for mycosis fungoides and Sézary syndrome.
2. While Kyowa Kirin believes that any possibility of double counting is small in view of the fact that the benefits of aSCT are long-term and affect overall survival outside the period measured in the MAVORIC trial, the company nevertheless provided a scenario analysis to explore “*excluding a proportion of the best responders, and therefore increasing the proportions of patients with partial response*” as requested by the ERG. This analysis was submitted to NICE on 5 June 2020, in response to the Technical Engagement Meeting, but while it confirmed that the adjustment made little difference to the calculations of OS used in the economic model, there is no indication that this has been taken into account by the Committee.
3. Furthermore, the issue of inclusion of aSCT also arose in another appraisal TA577 (brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma). The main clinical trial, in that appraisal, ALCANZA, permitted aSCT, although very few patients underwent transplant. The committee in TA577 accepted expert evidence that aSCT had become substantially more common in England since the date of the ALCANZA trial and that “*brentuximab vedotin could be used as a bridge to transplant for some patients whose disease adequately responds to treatment, but that there was uncertainty about the exact proportion in clinical practice*”. In these circumstances, the committee agreed that the proportion of patients undergoing aSCT incorporated in the economic model should be greater than that in ALCANZA.

Therefore, exactly the same issue arose in TA577, in relation to incorporation of aSCT in the economic model, as in the current appraisal of mogamulizumab, but a different approach was adopted. Paragraph 6.2.15 of the Methods Guide states:

“*In addition, as far as possible, the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals”.*

Kyowa Kirin believes that, in circumstances where no justification has been provided to support a different approach to incorporation of aSCT data between the two appraisals, this is unfair and inconsistent with the requirements of the Methods Guide.

The exclusion of aSCT from the economic analysis is therefore inconsistent with standard NHS practice in England and conflicts with the approach followed in another appraisal in similar circumstances. Finally, the company’s analysis demonstrating that the concerns held by the Committee regarding incorporation of aSCT are not material, has not been taken into account in reaching the conclusions in the FAD.

* 1. **The Committee’s conclusion that the IPCW-adjusted curve was not clinically plausible for the average person in the modelled population with severe disease is unexplained**

At paragraph 3.8 of the FAD, the Committee considers the method to be used to adjust for crossover in the standard care arm of the MAVORIC trial. Kyowa Kirin proposed use of the inverse probability of censoring weights (IPCW) method on the basis that this produced results consistent with external data. However, the Committee stated:

“*The committee was not convinced that the IPCW-adjusted curve was clinically plausible for the average person in the modelled population with severe disease.”*

No explanation is provided for this conclusion in the FAD and it cannot be understood by Kyowa Kirin. There is accordingly a lack of transparency, inconsistent with standards of procedural fairness.

While there is no explanation for the Committee’s conclusions, Kyowa Kirin is aware that the ERG expressed concern that there might be no plausible clinical explanation for an intermediate outcome in the IPCW method (an adjusted Kaplan Meier curve) that exhibited a significant drop in patients at risk at approximately 6 months. As explained by Kyowa Kirin, the drop in risk at 6 months is due to the MAVORIC trial design allowing patients to crossover only after two full cycles of treatment and an additional minimum 2 weeks waiting period. As a result, there is a high number of patient switching occurring at the time resulting in the drop in the curve, while subsequently the rate of switching is lower, leading to a smoother curve afterwards. The abrupt drop arises as the probability of survival is only re-estimated when there is a death, despite the weights varying continuously. In summary, the drop is a statistical artefact of the trial protocol, how the Kaplan-Meier curve is generated and the IPCW re-weighting so requires no clinical explanation. The FAD does not suggest that the Committee was concerned by the statistical artifact (if it had, Kyowa Kirin would have been able to address the point), but we mention it for completeness.

In summary therefore, the Committee’s conclusion at paragraph 3.8, include no reasons for the concern that the IPCW-adjusted curve might not be clinically plausible, therefore preventing Kyowa Kirin from addressing these issues. The statement in the FAD is particularly surprising, given the fact that the results of the IPCW adjustment are consistent with external clinical evidence provided to the Committee. In these circumstances the statement by the Committee lacks transparency and is procedurally unfair.

* 1. **The Committee’s decision not to include carer utilities in the economic model is based on conclusions which are inconsistent with NICE’s Methods Guide and inadequately explained**

At paragraph 3.12 of the FAD, the Committee decides not to include carer utilities in the economic model, despite accepting the very substantial burden placed on carers as a result of caring for someone with mycosis fungoides or Sézary syndrome. The Committee’s reasons appear to be:

* It found the utility gain proposed for carers by Kyowa Kirin to be “*implausibly large*” compared with the expected utility gain for people with the condition; and
* It criticised the method used by Kyowa Kirin to obtain data on carer utilities, which used vignettes in the general population, on the basis that this “*was not in line with NICE’s guide to the methods of technology appraisal*”.

However, the Committee provides no reasons for its conclusion that the utility gain proposed for carers in this appraisal was *“implausibly large”*. It is accepted that carers caring for someone with mycosis fungoides or Sézary syndrome experience a particularly large utility decriment as a result of the nature of the disease, the physical disfigurement and social isolation as a result and the requirement for intensive and burdensome nursing support to manage skin lesions. The ERG agreed that the utility values and the implementation proposed by Kyowa Kirin were both conservative and appropriate. In these circumstances, the Committee should explain why it rejects the utility gain proposed by Kyowa Kirin based on the studies conducted.

The FAD suggests that NICE’s Methods Guide advises against incorporation of carer utilities or against use of vignettes in the general population for the purposes of assessing carer utilities. This is not however the case. NICE’s Methods Guide states that the perspective on outcomes includes ‘*all direct health effects, whether for patients, or when relevant, carers*’. There is therefore quite explicitly no prohibition on including carer utilities in the economic modelling even though the Methods Guide includes no specific guidance on how this should be achieved. This is consistent with the fact that carer utilities have been incorporated in multiple previous appraisals

* 1. **The Committee’s conclusion that mogamulizumab is not considered to be a life-extending treatment at the end of life relies on evidence which has not been disclosed and is therefore unfair**

At paragraph 3.13 of the FAD, the Committee relies upon “*the professional organisations’ response to technical engagement*” to support a conclusion that mogamulizumab is not a life-extending treatment at the end of life. Paragraph 3.13 states that the professional organisations indicated that “*median survival for people with disease stage 2B and above eligible for second-line treatment in the NHS was estimated to be between 3 to 5 years*”.

Kyowa Kirin is unaware of any response by professional organisations or any other consultee in this appraisal, consistent with the quotation in the FAD. We therefore assume that such evidence has not been disclosed for proper consideration by consultees. In the absence of proper disclosure, Kyowa Kirin is unable to test the reliability of the material relied upon or to participate appropriately in this appraisal. Such lack of transparency is inconsistent with standards of procedural fairness and constitutes a deficiency in the process followed in this appraisal. (The alternative interpretation, which is that the Committee has misinterpreted the submissions by clinical experts, is addressed at appeal point 2.5 below.)

* 1. **The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal do not take into account the factors identified at paragraph 6.3.3 of NICE’s Guide to the Methods of Technology Appraisal**

At paragraph 3.14 of the FAD, the Committee refers to NICE’s Guide to the Methods of Technology Appraisal (“the Methods Guide”) to note that “*above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality adjusted life year (QALY) gained, judgments about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER*.” However, the Committee has not seemingly considered uncertainty, or the other factors identified in the Methods Guide in the way required by NICE’s procedures.

The Methods Guide lists, at paragraph 6.3.3, a number of factors to be taken into account when considering an ICER above £20,000 per QALY gained. While these factors include uncertainty, they also include:

* Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.
* The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.
* The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'
* Aspects that relate to non-health objectives of the NHS.

There is however no indication at paragraph 3.14 of the FAD that any of these factors have been taken into account by the Committee, even though mogamulizumab scores very highly on some or all of them. In particular mogamulizumab:

1. is associated with benefits not taken into account in the economic model including: improvements in the health-related quality of life experienced by carers and the possibility of providing a bridge to aSCT after current treatment and, as confirmed in TA577, the EQ5D (NICE’s preferred measure for assessing quality of life across appraisals does not reflect key elements (such as pruritis) relevant to skin disorders in general and this appraisal in particular);
2. is innovative, as recognised at paragraph 3.17 of the FAD, (it was, in fact, granted “promising innovative medicine”(PIM) status by MHRA); and
3. meets, at least potentially, the definition of a 'life-extending treatment at the end of life' .

The fact that none of these matters have been considered by the Committee in determining the appropriate ICER threshold at paragraph 3.14 (or, in any event , if they have been considered, there is no explanation in the FAD as to how they have been taken into account and weighed by the Committee in reaching its conclusions in this paragraph) represents a procedural deficiency in this appraisal. The ICER threshold is clearly of fundamental importance in any appraisal and in cases where, controversially, the Committee concludes that the top of the threshold should be reduced, it is necessary that this decision is appropriately considered in the context of the factors listed in NICE’s Methods Guide and the assessment of each factor is adequately explained, so that consultees understand the basis for the decision and whether it is reasonable. In this case however, the requirements of the Methods Guide do not seem to have been met or if they have the decision-making process lacks transparency.

* 1. **The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal do not assess uncertainty in accordance with paragraph 6.2.16 of NICE’s Guide to the Methods of Technology Appraisal**

As stated in the previous appeal point, at paragraph 3.14 of the FAD, the Committee considers the appropriate ICER threshold for this appraisal and, based on “*the high level of uncertainty associated with the MAVORIC analysis*” concludes that “*an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)*.”

However, the Methods Guide specifies, at paragraph 6.2.16, the approach to uncertainty that the Committee is required to adopt:

“*The Appraisal Committee is likely to consider more favourably technologies for which evidence on cost effectiveness is underpinned by the best-quality clinical data than those for which supporting evidence is dependent to a large extent on theoretical modelling alone. However, the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases”*.

Mogamulizumab is used to treat ultra-orphan diseases, where inevitably the evidence base is limited and, in circumstances where there is no generally accepted standard of care, there are likely to be challenges extrapolating international clinical trials to the care provided specifically in England. The MAVORIC trial however is the largest clinical trial ever conducted in any subgroup of patients with CTCL. It is the first phase III trial to include patients with Sézary syndrome and provides outcomes for the largest number of Sézary syndrome patients ever to be included in a randomised controlled clinical trial. The results from MAVORIC were supplemented, for the purposes of this appraisal, by data from the HES database which includes real world evidence from England on outcomes of all patients with mycosis fungoides and Sézary syndrome in England over an 10 year period. In the context of such rare diseases, the data available for this appraisal are therefore exceptional.

However there is no indication in paragraph 3.14 of the FAD that the Committee gave any consideration to the rarity of mycosis fungoides and Sézary syndrome when considering uncertainty and the data submitted in this appraisal, as it was required to do in accordance with paragraph 6.2.16 of the Methods Guide. If it did give such consideration, this is not stated and no explanation of the Committee’s assessment is provided in the FAD.

The issue raised in this point of appeal raises a fundamental point of principle. Treatments for rare diseases will almost inevitably be associated with uncertainty. An approach which simply reduces the ICER threshold for such therapies is contrary to the public policy considerations underpinning the orphan drug regime and disadvantages patients suffering from these rare disorders, particularly those suffering from the ultra-rare diseases, such as those considered in this appraisal.

* 1. **The Committee’s conclusions regarding the appropriate ICER threshold for this appraisal lack transparency**

While the Committee concludes at paragraph 3.14 of the FAD that the ICER threshold for this appraisal “*would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)*” it does not specify the precise value of the threshold applicable in this case. Furthermore, while Kyowa Kirin has requested clarification from NICE as to the applicable threshold value, no further information was provided, save that the company has been informed that it should not assume that the relevant number was any specific figure towards the middle of the range.

This is procedurally unacceptable and unfair. Whatever ICER threshold is determined by the Committee to be applicable, following its proper assessment in accordance with NICE’s Methods Guide, should be stated transparently, together with an explanation of how the figure was calculated. It is a fundamental part of a fair procedure that a person, such as Kyowa Kirin, affected by a decision understands what it has to do in order to achieve a positive outcome and can confirm that decision-making is reasonable and not arbitrary. Communication of the relevant ICER threshold applied by the Committee is central to those requirements. In the absence of such information, Kyowa Kirin is unable to determine what it has to do in order to obtain a positive recommendation for use of mogamulizumab by the NHS in England. Such lack of transparency is not in the interests of patients, clinicians or the NHS and it is not procedurally fair.

* 1. **The Committee’s conclusions regarding the most plausible ICER for this appraisal lack transparency**

The Committee’s conclusions regarding the cost-effectiveness estimates for this appraisal are provided at paragraph 3.15 of the FAD. The Committee states:

“*The committee considered both [*the HES analysis and the MAVORIC analysis] *to be associated with uncertainty and so considered ICERs from both approaches for its decision making. It understood that, after taking into account all of its preferred assumptions, the most plausible ICER was £33,043 per QALY gained based on HES data and between £42,812* [IPCW adjustment method] *and £80,555* [2-stage estimation method] *per QALY gained based on MAVORIC data”.*

Accordingly, the most plausible ICER assessed by the Committee is between £33,043 and £80,555 per QALY gained. In circumstances where mogamulizumab is a treatment for ultra-orphan diseases, there will inevitably be some uncertainty in relation to the data. However, the Committee’s conclusions involving a very wide ICER range, are procedurally unacceptable. The Committee must, consistent with rigorous decision-making and as a matter of fairness, make a proper determination (not a range of over £50,000 per QALY gained, where the upper limit is more than double the lower limit) as to the most plausible ICER, explaining its reasons.

This determination is required so that stakeholders know what the Committee’s conclusions are and can test whether they are reasonable. As indicated earlier in this appeal, the quantity of data available in this appraisal is exceptional for a treatment for an ultra-rare disease and Kyowa Kirin has made every effort to co-operate with NICE in order to provide the analyses which would allow it to issue a positive recommendation in the interests of patients. The effective difference between the upper and lower bounds of the range set out in paragraph 3.15 of the FAD, is however currently so large that it precludes sensible engagement by the company. It is not only a requirement of a fair procedure, it is in the interests of all stakeholders that the most plausible ICER is adequately defined in the FAD. That requirement has not been met by the current FAD for mogamulizumab.

* 1. **The Committee’s statement that the relevant benefits associated with mogamulizumab could be adequately captured in the model disregards its own conclusions, is inconsistent with NICE’s procedures and lacks transparency**

At paragraph 3.17 of the FAD, the Committee recognises that mogamulizumab is innovative, but concludes “*that the relevant benefits associated with mogamulizumab could be adequately captured in the model*”.

The test, so far as paragraph 6.3.3 of the Methods Guide is concerned, is whether the relevant benefits have in fact been captured in the assessment of cost-effectiveness, not whether they “*could be*” captured, as stated in the FAD. The reason for consideration of whether the relevant benefits have been captured is so that the Committee can form a proper view about whether the calculated ICER is likely to be an under-estimate and make appropriate adjustments in its overall conclusions. To document that relevant benefits “*could be*” captured even though a decision has been made that they should be excluded, is inconsistent with the purpose of the review and the requirements of the Methods Guide.

(a) **Failure to take into account relevant benefits of mogamulizumab not included in the economic model.**

In this case, the determination by the Committee to take into account “*relevant”* benefits of mogamulizumab not currently captured in the economic model conflicts with:

* Its conclusion at paragraph 3.7 of the FAD that some people may undergo aSCT after initial treatment and removing this from the model had a “*small effect*” on the cost-effectiveness estimates;
* Its recognition at paragraphs 3.12 and 3.17 of the FAD that carer utilities should be removed from the base case analysis despite “*the burden placed on some carers*”
* The fact that, as explained at page 125 of Kyowa Kirin’s original submission. the benefits of mogamulizumab in terms of health-related quality of life are not fully captured in the EQ5D (the measure preferred by NICE) - an issue not addressed by the Committee at all in the FAD, even though it was taken into account by the committee that considered the appraisal of brentuximab vedotin, TA 177 for mycosis fungoides.

Accordingly, in reaching its conclusions at paragraph 3.17, the Committee has failed adequately to take into account relevant evidence. Furthermore, if the Committee had taken into account the matters listed above, its conclusion would have been that the Committee’s assessment of the most plausible ICER for mogamulizumab was substantially pessimistic.

(b) **Failure to reach any conclusion in relation to the incorporation of carer utilities on the basis that “*all cost-effectiveness estimates, even those including a carer utility gain in the model, were much higher than the middle of the range normally considered to be cost effective”*.**

The wording of paragraph 3.17 of the FAD indicates that the Committee concluded it had no obligation to reach a conclusion in relation to the impact of including carer utilities in the economic model, despite agreeing that such benefits were relevant in the context of this appraisal. The reason for this conclusion is stated to be that, even including carer utilities, the ICER would still be above the threshold range determined for this appraisal.

Such a conclusion is, however, inconsistent with rigorous decision making and procedurally unfair. It does not allow Kyowa Kirin (or any other stakeholder) to test the validity of the Committee’s determination in relation to carer utilities or to understand the impact of this element of the appraisal on the ICER as accepted by the Committee. Importantly, even if the cost effectiveness estimate incorporating carer utilities (and potentially other matters raised in this appeal) is above the threshold range for this appraisal (the level of which is an issue challenged in this appeal), Kyowa Kirin is entitled to be informed how much above the threshold the most plausible ICER falls. This is a basic requirement of procedural fairness, so that a person affected by a decision understands what they have to do in order to achieve a positive outcome. It is also plainly in the interests of patients, clinicians and the wider NHS.

1. **GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE**
   1. **The Committee’s conclusion that Kyowa Kirin’s analysis using the Hospital Episodes Statistics (HES) database was not adequately matched to the data from the MAVORIC trial is incorrect and therefore unreasonable**

At paragraph 3.5 of the FAD, the Committee refers to the indirect treatment comparison comparing mogamulizumab outcomes from the MAVORIC trial with real world data from the Hospital Episodes Statistics (HES) database and concludes:

“*It noted that the MAVORIC data were only matched to the HES data for the proportion of people with mycosis fungoides and Sézary syndrome. Age (a known prognostic factor) and sex (which can potentially affect survival) were not matched. This was because the company considered that these were similar between the MAVORIC and HES data and wanted to avoid reducing the sample size unnecessarily*”.

The Committee notes the view of the ERG that age and sex should have been matched and lists other factors, including “*stage of disease*” which it stated were not available in the HES database and could not be matched. The Committee relied upon these matters to conclude that the “*limitations of the data, the lack of information on prognostic factors and the difficulty in assessing its reliability meant that the HES analysis results were uncertain*”.

The Committee also refers to the HES analysis at paragraph 3.14 of the FAD where it states that the HES analysis was “*associated with uncertainty*” and relies on the fact that the ERG said it “*could not assess the reliability of the HES analysis and because of data limitations, only 1 prognostic factor had been matched…*..”

However the conclusions of the Committee are incorrect. In particular:

* While the Committee stated that only one prognostic factor had been matched, the patients from the HES data used in Kyowa Kirin’s analysis were matched for the following prognostic factors:
  + Stage of disease (using type of treatments and place of treatment as proxy)
  + Number of prior systemic therapies
  + Prior systemic therapies
* In addition, a matching adjusted comparison (MAIC) was conducted in relation to disease states in the two groups (i.e. the distribution of mycosis fungoides and Sézary syndrome)
* Furthermore, while the Committee states that the age and sex of patients in MAVORIC and HES were not matched, this was assessed by Kyowa Kirin and viewed as unnecessary as these characteristics were similar in the pre and post matched groups:
  + Mean age in MAVORIC was 63 and in HES was 65.
  + Mean age post matching was 60.48 in MAVORIC and 65 in HES
  + Percentage males was 58% in MAVORIC and 62% in HES
  + Percentage males post matching was 61.4% in MAVORIC and 62% in HES.
* While the Committee states that disease stage could not be matched and Kyowa Kirin’s conclusions in relation to performance status, haematological, hepatic and renal function were unsupported by evidence, this disregards clinical expert evidence that:
  + While disease stage was not documented in HES, the fact that patients were treated in secondary care with systemic treatments creates a strong inference of advanced disease.
  + While performance status and haematological, hepatic and renal function were not recorded in HES, the fact that patients were deemed eligible for systemic treatment indicates performance score of 1 or less and satisfactory haematological, hepatic and renal function.
* Finally, while the Committee notes that “the ERG considered that insufficient information had been provided on the methodology of the unanchored indirect comparison to assess the reliability of the results”, Kyowa Kirin provided detailed information in response to a request from the ERG on 27 November 2020; no additional queries were raised by the ERG.

In summary therefore, the Committee’s reasons for concluding that the HES analysis results were uncertain are based on errors of fact. In particular, the Committee states that: only one variable was matched, whereas four variables were matched using different techniques and two variables were considered but did not require matching; and the Committee’s statement that Kyowa Kirin’s conclusions were unsupported by evidence, disregards the opinions of experts. The decision of the Committee in relation to the reliability of the HES analysis is therefore unreasonable.

* 1. **The Committee’s reliance on the two-stage estimation method to produce overall survival estimates for survival in the standard care arm of the MAVORIC trial is inconsistent with the available evidence**

At paragraph 3.8 of the FAD, the Committee considers the methods proposed by Kyowa Kirin and the ERG to adjust for crossover between the treatment groups in the MAVORIC trial. These method chosen makes a material difference to the estimation of overall survival in the standard care arm of the trial, excluding the effects of crossover, and is therefore of substantial importance to the assessment of treatment benefit with mogamulizumab and cost effectiveness.

1. **The 2-stage estimation method is not supported by data from observational studies and expert evidence**

To address the issue of crossover in the standard care arm of the MAVORIC trial, Kyowa Kirin proposed use of the inverse probability of censoring weights (IPCW) method which produces estimates consistent with:

* Data obtained from the HES database, which includes all patients with mycosis fungoides and Sézary syndrome, treated in NHS secondary care in England in the last 10 years (198 patients) and provides the most reliable information regarding outcomes of patients with mycosis fungoides or Sézary syndrome who have received at least 1 prior systemic therapy in England.
* The results of relevant observational studies, which document overall survival from diagnosis of advanced disease:
  + Kim YH et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003; 139(7): 857-866
  + Agar NS et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/ European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010; 28(31): 4730-4739. Considered 1,502 patients over the period 1980-2009.
  + Talpur R et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. Clin Cancer Res 2012; 18(18): 5051-5060
* Clinical expert opinion -
  + Submitted by Kyowa Kirin from three UK clinical experts with experience in the disease and with mogamulizumab
  + Professor Scarisbrick and Dr Gallop-Evans at the 2nd Committee Meeting

In contrast, the ERG proposed use of the 2-stage estimation method, which produces estimates inconsistent with the available evidence.

This is demonstrated by the level of external support for the two adjustment methods shown in the table below

**Comparing overall survival demonstrated in observational studies with data obtained from MAVORIC and adjusted using the IPCW or 2-stage estimation methods**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Median survival for advanced patients from:** | **Source** | **Median survival** | **Details** | **Comments** |
| **From diagnosis** | Kim et al. 2003 | 1.5-4.0 years depending on stage | stage IIB/III: 4.0 years, IV: 1.5 years | With lower proportion of stage IV patient, less heavily pre-treated, smaller proportion of SS than MAVORIC trial population |
| Agar et al. 2010 | 1.4-4.7 years depending on stage | stage IIB and IIIA: 4.7 years, IIIB: 3.4 years, IVA1: 3.8 years, IVA2: 2.1 years, IVB: 1.4 years |
| Talpur et al. 2012 | ~5 years | From Kaplan-Meier graphs |
| Scarisbrick et al. 2015 | 5.3 years | - |
| HES database | ~6 years | SS: 2.6 years MF: not reached, 58% surviving at 6 years | Less heavily pre-treated, smaller proportion of SS than MAVORIC trial population |
| **From the start of 2nd line systemic treatment** | HES database | 1.5 years | - | With smaller proportion of SS than MAVORIC trial population |
| **From the start of 2nd+ line systematic treatment** | For vorinostat arm from MAVORIC adjusted with IPCW | 1.8 years | - | - |
| For vorinostat arm from MAVORIC adjusted with 2-stage estimation | 3.4 years | - | - |

Overall, the data from observational studies, including real world evidence from NHS practice in England from the HES database, consistently suggest a median overall survival for patients with advanced mycosis fungoides and Sézary syndrome of:

* around 5 years from diagnosis; and
* around 1.5 years from the time at which they receive second line systemic treatment (the time relevant to this appraisal).

This is entirely consistent with the evidence of clinical experts, Professor Scarisbrick and Dr Gallop-Evans (see Questions for Clinical Expert document and evidence given at Appraisal Committee meetings) and also with the results of the IPCW adjustment method for the vorinostat arm of MAVORIC.

Similarly, the survival curve from the IPCW adjusted comparator arm from the MAVORIC trial overlaps with the survival curve from the HES database, while the survival curve from the 2-stage estimation adjusted comparator arm from the MAVORIC trial is substantially higher.

Furthermore, when the 2-stage estimation method is applied to the data from the standard care arm of MAVORIC, this produces results that substantially exceed the figures produced by observational studies for patients receiving second line systemic treatment and conflict with expert evidence.

1. **The 2-stage estimation method assumes a disease modifying effect of standard care/ subsequent treatments**

The 2-stage estimation method results in greater post-progression survival in patients treated with standard care than those treated with mogamulizumab. There is no evidence to support such a conclusion and this is clinically implausible. It also contrasts with the result from MAVORIC trial, that shows substantially longer time on subsequent treatment after mogamulizumab than with the comparator (7.7 months vs. 3.24 months respectively), and the clinical expert opinion submitted by Kyowa Kirin. However, while this situation has been drawn to the attention of the Committee there is no evidence that it has recognised the issue or taken it into account when concluding that the 2-stage estimation method provides an appropriate basis for decision-making in this appraisal.

However, despite the lack of evidence supporting use of the 2-stage estimation method and the fact that it conflicts with external evidence and produces results that are counter-intuitive, the Committee gave equal weight to the two crossover adjustment methods, concluding “*the results from the 2-stage estimation and IPCW methods represented the upper and lower range of plausible overall survival in the standard care arm*” . In circumstances where the IPCW method produces results supported by extensive external evidence, whereas the 2-stage estimation does not, the results of the latter cannot be considered plausible and the Committee’s conclusion is unreasonable.

* 1. **The Committee’s conclusions regarding the disease-modifying effects of mogamulizumab disregard expert evidence and misinterpret the evidence of one patient expert and are therefore unreasonable**

At paragraph 3.8 of the FAD, the Committee notes that the IPCW method proposed by Kyowa Kirin to adjust for patient crossover in the MAVORIC trial, assumes continued benefit on subsequent treatments after mogamulizumab. The Committee subsequently concludes that it “*was not convinced that mogamulizumab provided a prolonged benefit after disease progression and could be considered disease-modifying*”. However, in reaching that conclusion, the Committee disregarded relevant evidence, and misinterpreted the evidence of one of the patient experts.

(a) **Clinician interviews from experts treating CTCL and with experience using mogamulizumab in the NHS were submitted to NICE and confirmed the view that mogamulizumab exerts a disease modifying effect**

The following clinical expert opinions were submitted to NICE and have seemingly been disregarded by the Committee:

* “Mogamulizumab has a better response rate and longer duration of response. The hypothesis is, that even if the patient has progressed, the disease became indolent. That is, even if the disease has crossed the threshold for the progression criterion, the disease was slower after mogamulizumab”.
* “Mogamulizumab has a potential benefit post-progression as it is disease modifying”.
* “Additionally, mogamulizumab changes the underlying biology of the disease, e.g. there is anecdotal evidence that when the disease comes back, it does so in a modified and slower way”.

**(b) The “time to next treatment” (TTNT) analysis from MAVORIC presented in Kyowa Kirin’s original submission to NICE[[1]](#footnote-2) confirmed that TTNT was significantly longer for mogamulizumab compared with vorinostat and more than double that recorded historically for systemic treatments (11.0 versus 5.4 months[[2]](#footnote-3)).**

This evidence is not referenced in the FAD and has presumably been disregarded.

**(c) The FAD refers to and misinterprets the evidence of one patient expert:**

*“One patient expert described how their symptoms slowly returned after mogamulizumab was temporarily stopped for around 12 weeks”*

This evidence confirms that the patient experienced continued, albeit reducing, benefit of mogamulizumab after treatment was discontinued.

Furthermore, the Committee disregarded the fact that the account of the patient expert is inconsistent with the assumption inherent in the 2-stage estimation method of adjustment, that all benefits of mogamulizumab discontinue immediately once treatment is discontinued and patients deteriorate more quickly that if they had not received such treatment.

In summary therefore, the Committee has disregarded evidence supporting a disease modifying effect of mogamulizumab without providing any reasoned explanation and has misinterpreted the evidence of the patient expert in formulating its conclusions, which are therefore unreasonable.

* 1. **The Committee’s conclusion that it was not convinced that mogamulizumab provides an overall survival benefit is unreasonable in light of the evidence available**

The Committee states, at paragraph 3.9 of the FAD:

“*The committee was not convinced that mogamulizumab provided an overall survival benefit compared with standard care”*.

However, all evidence and scenarios presented to the Committee demonstrate an OS benefit relative to standard care and the Committee itself has accepted, elsewhere in the FAD, that this is the position. Therefore, at paragraph 3.8 of the FAD, the Committee states;

“ *the committee concluded that the results from the 2-stage estimation and IPCW methods represented the upper and lower range of plausible overall survival in the standard care arm*”.

Accordingly, even using the most unfavourable estimation method accepted by the Committee for the standard of care arm from MAVORIC and taking into account the available data on overall survival in patients treated with mogamulizumab (as reported e.g. in Kyowa Kirin’s original submission at Appendix J, tables J1 and J3), extrapolated using the exponential distribution preferred by the Committee in paragraph 3.9 of the FAD, this results in in an overall survival advantage of 1.57 years associated with mogamulizumab compared to standard care

It is also relevant to consider that the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded:

“*There are no uncertainties in the favourable effects for mogamulizumab in the treatment of MF and SS.”*

In the above circumstances, the Committee’s conclusion at paragraph 3.9 of the FAD, , that it was not convinced that mogamulizumab produces any OS benefit relative to standard care, which disregards its own conclusions as well as the evidence submitted, is unreasonable.

* 1. **The Committee’s conclusion that mogamulizumab is not considered to be a life-extending treatment at the end of life relies on incorrect and irrelevant data and is therefore unreasonable**

At paragraph 3.13 of the FAD, the Committee concludes that mogamulizumab is not a life-extending treatment at the end of life. In support of that conclusion, the Committee relies upon evidence, which it construed as indicating that the median life expectancy in patients with advanced mycosis fungoides or Sézary syndrome, after at least one systemic therapy who are eligible for treatment with mogamulizumab, but who receive standard care, exceeds two years.

However, in at least two instances, the evidence relied upon by the Committee for this conclusion is irrelevant in the context of the current appraisal or has been misquoted.

* The Committee refers to a study by the Cutaneous Lymphoma International Consortium (Scarisbrick J et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol 33: 3766-3773) in which the “*median overall survival for people with advanced mycosis fungoides and Sézary syndrome was 63 months*”.

However, the criteria for inclusion in this study were diagnosis with stage IIB-IV mycosis fungoides or Sézary syndrome after 2007 and the median OS figure of 63 months represents time from diagnosis in the trial population. This does not reflect the population of patients eligible for treatment with mogamulizumab, who have not just been diagnosed but have all undergone prior treatment for their condition. It is self-evident that survival for patients in the Cutaneous Lymphoma International Consortium study will be materially longer than that for patients eligible for treatment with mogamulizumab.

The Committee stated that “*the people in the study were from specialist centres so the large difference in survival compared with the HES analysis was concerning*”. Therefore, not only were survival data from diagnosis in the Cutaneous Lymphoma International Consortium study irrelevant to the consideration of mogamulizumab by the Committee, the fact that the Committee questioned the HES analysis based on these data was unreasonable. (For completeness, it is relevant to note that survival from diagnosis of advanced disease in the CTCL study (5.3 years) and the HES database (around 6 years) were similar.)

* The Committee also refers to “*the professional organisations’ response to technical engagement*”, stating that “*median survival for people with disease stage 2B and above eligible for second-line treatment in the NHS was estimated to be between 3 to 5 years*”.

However the Committee appears to have incorrectly referenced and misquoted the evidence of the clinical expert, who answered the question “*In your clinical experience, what is the current expected survival time for people with MF and SS after at least 1 prior therapy?*” as follows:

“*For people eligible for second-line treatment this would be around 1 year to 18 months and for people eligible for third-line treatment, this would be around 6 months or less. The survival time from diagnosis is around 3 to 5 years.*”

Assuming the clinical expert’s responses formed the basis for the evidence referenced in paragraph 3.13 of the FAD (and we are aware of no other statements which refer to 3-5 year survival), the Committee has either erroneously disregarded the overall survival relevant to patients eligible for treatment with mogamulizumab or mistakenly relied upon the survival for patients from diagnosis. [ The alternative possibility that NICE has simply failed to disclose the data relied upon by the Committee is addressed at appeal point 1.4 above.]

In summary it is inappropriate and unreasonable to rely on data relating to OS from diagnosis in the context of the current appraisal of a second line systemic treatment and this will result in an incorrect extension to the OS benefit. Therefore the use of the study by the Cutaneous Lymphoma International Consortium and the evidence of the clinical expert, as interpreted by the Committee, to support a conclusion that mogamulizumab is not a life extending treatment at the end of life, is inappropriate and unreasonable as explained above. The importance of this issue in the context of this appraisal is demonstrated by the Committee’s summary of its conclusions at the end of paragraph 3.13 of the FAD which refer to the Cutaneous Lymphoma International Consortium study and the evidence of the clinical expert , as two of the three sources of evidence which cause it to question the HES data proposed by Kyowa Kirin confirming the eligibility of mogamulizumab under NICE’s End of Life criteria.

**THE DETERMINATION OF THIS APPEAL**

Kyowa Kirin requests that this appeal should be determined at an oral hearing.

**REQUESTED OUTCOME FOLLOWING APPEAL**

Kyowa Kirin respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:

* To reconsider in accordance with NICE’s Methods Guide and provide clarity in relation to:
  + The ICER threshold for this appraisal;
  + The most plausible ICER calculated by the Committee
  + The effect on the most plausible ICER of any factors which are not reflected in the economic model;
* To use the IPCW method to adjust for patient crossover in the standard of care arm of the MAVORIC trial;
* To reconsider the HES data based on the matching with MAVORIC which was undertaken by Kyowa Kirin
* To include aSCT in the economic model unless there is a valid reason for diverging from the approach adopted in TA577;
* To include carer utilities in the economic model or explain why these are considered clinically implausible;
* To reconsider the application of the life expectancy criterion in the end of life criteria based on median survival in patients eligible for second line therapy and not survival from diagnosis.

1. Page 82 [↑](#footnote-ref-2)
2. Hughes CF et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sézary syndrome : a comparative study of systemic therapy. Blood 2015; 125(1): 71-81. [↑](#footnote-ref-3)