Professor Tim Irish

Chair Appeal Committee

The National Institute for Health and Care Excellence (NICE)

10 Spring Gardens

London

SW1A 2BU

12th April 2021

Dear Professor Irish

**Appeal against the Final Appraisal Document for mogamulizumab for previously treated mycosis fungoides and Sézary syndrome**

Thank you for your letter dated 25 March 2021, in which you set out your preliminary views regarding the admissibility of the points of appeal advanced by Kyowa Kirin and set out in the Notice of Appeal submitted on 18 March 2021. We now respond to your preliminary view of our appeal, addressing those points where you suggest, following initial review, either that these should be considered under a different ground or that they may not constitute valid points of appeal. For the avoidance of doubt, we provide no further submissions in relation to those points of appeal which you agree should proceed to a hearing.

1. **Ground 1**
   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**

Noted

* 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**

You express the preliminary view that this is not a valid appeal point on the cumulative basis of the following conclusions :

1. The suggestion that “*standards of procedural fairness do not require the Committee to explain the reasons behind every statement or even every issue resolved in the FAD*”;
2. That “the FAD and the committee papers as a whole provide intelligible and adequate reasons which enable the appellant to understand why the recommendation was made as it was and what conclusions were reached on the principal issues”; and
3. Your view that “the IPCW-adjusted curve was not clinically plausible was the reason which the committee was obliged to give and fairness does not require reasons for reasons”.

Kyowa Kirin’s response

We address each of the issues you have raised below:

1. NICE’s Guide to the Methods of Technology Appraisal, states at paragraph 3.1.1:

“*To ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and analysis, and their interpretation are of the highest standard and are transparent*”.

While it may not be necessary for the Committee to explain the reasons underpinning every minor conclusion in the FAD, procedural fairness plainly requires that transparent explanations are provided in relation to all the more important decisions made by the Committee. In a recent decision, the Court of Appeal has stated that reasons must “*enable the reader to understand why the matter was decided as it was and what conclusions were reached on the “principal important controversial issues*”[[1]](#footnote-1).

The choice of method used to adjust for crossover in the standard care arm of the MAVORIC trial is of critical importance in this appraisal and may solely determine whether mogamulizumab is ultimately recommended for use by NHS patients in England and Wales. Therefore, any conclusion by the Appraisal Committee to reject the approach proposed by the company in favour of an alternative must be appropriately explained.

1. We firmly maintain that it is procedurally incorrect to consider “*the FAD and Committee papers as a whole*” when seeking to understand the reasons for the Committee’s guidance. The Committee papers comprise submissions by a range of individuals and bodies who are, importantly, not the decision makers in relation to an appraisal. The Appraisal Committee is the decision maker and the only document which sets out the conclusion of the Appraisal Committee is the FAD. The FAD therefore, is the only document which can explain the Committee’s reasons for its decisions. The Committee papers provide no assistance in this respect, unless they are explicitly referenced in the FAD to justify a conclusion by the decision maker on a specific point.
2. The issue raised by Kyowa Kirin in this point of appeal is not one of providing “*reasons for reasons*”, but rather goes to the adequacy of the reason provided. The requirement for reasons is a part of procedural fairness in order to ensure that Kyowa Kirin understands why its application in respect of mogamulizumab has been unsuccessful and to verify that decision making has been rational. In the absence of any explanation for the conclusion that “*the IPCW-adjusted curve was not clinically plausible*”, the statement is uninterpretable and cannot be tested. The level of reasoning is inadequate and inconsistent with the high standards and transparency to which NICE is committed (see paragraph (a) above).

In summary, transparency is a key component of procedural fairness and this requires not simply the provision of reasons, but that the reasons provided are adequate and comprehensible. The choice of method used to adjust for crossover in the standard care arm of the MAVORIC trial is of fundamental importance in the context of this appraisal and a high level of reasoning is required to explain the Committee’s conclusions, as set out in the FAD. However the Committee’s rejection of the IPCW method on the basis of clinical implausibility is an unexplained assertion; this is not adequate reasoning because it prejudices Kyowa Kirin’s ability to understand the Committee’s decision and respond to it. If the Committee had provided adequate reasons, which Kyowa Kirin believed to be unreasonable (or had no reasons for its conclusion), it would be open to the company to appeal the decision under Ground 2. However, the current situation is simply one of lack of transparency, a procedural deficiency which is properly brought under Ground 1.

* 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**

You suggest that this point of appeal should not proceed under Ground 1 on the basis that:

1. You do not consider that Kyowa Kirin’s case that the Committee should have provided reasons/ explanation for its conclusion that carer utilities proposed by the company are “*implausibly large*” is arguable, for the same reasons as those in relation to appeal point 1.2; and
2. You say that any misunderstanding of or failure to follow NICE’s Guide to the Methods of Technology Appraisal is not arguable as the Methods Guide does not prescribe whether or how the Committee must incorporate carer utilities in its modelling and the Committee recognised the burden placed on some carers.

Kyowa Kirin’s response

Our response to your preliminary view is as follows:

1. The submissions made in relation to appeal point 1.2 are repeated.

* The incorporation of carer utilities is, like the IPCW adjustment considered at appeal point 1.2, a key issue in the context of this appraisal and the Committee’s decision not to incorporate such benefit of mogamulizumab in the economic modelling, despite recognising the burden placed on carers, makes a material difference to the ICER calculation. The carer utilities proposed by Kyowa Kirin were supported by evidence and agreed by the ERG; in these circumstances the conclusion by the Committee that such utilities are “implausibly large” requires explanation and the failure to provide any reasoning constitutes an unacceptable lack of transparency.
* With respect to your view that Kyowa Kirin should consider “*the FAD and Committee papers as a whole*” when seeking reasons for the Committee’s conclusions, the submissions under section 1.2 paragraph (b) are applicable in their entirety.
* Again, this is not a question of providing “*reasons for reasons*”, but to the fact that the reasoning provided in this case was inadequate. In the absence of any explanation for the Committee’s conclusion that the carer utilities proposed by Kyowa Kirin were “*implausibly large*”, the statement is uninterpretable and cannot be tested. The level of reasoning was therefore inconsistent with the high standards and transparency to which NICE is committed (see submissions under section 1.2 paragraph (a) above).
* For the avoidance if doubt, if the Committee relies upon any evidence in support of its position, transparency also requires that this is disclosed for consideration by stakeholders, including Kyowa Kirin.

In summary, a simple assertion that the carer utilities proposed by Kyowa Kirin are “implausibly large”, without explanation, despite evidence to the contrary and ERG support is unacceptable. As stated in relation to appeal point 1.2, such an approach is not adequate because it prejudices Kyowa Kirin’s ability to understand the Committee’s decision and respond to it. If the Committee had provided adequate reasons, which Kyowa Kirin believed to be unreasonable (or had no reasons for its conclusion), it would be open to the company to appeal the decision under Ground 2. However, the current situation is simply one of lack of transparency, a procedural deficiency which is properly brought under Ground 1.

1. The issue raised by Kyowa Kirin is that the Committee has stated that the company’s approach is not consistent with the Methods Guide, when this is not correct.

At paragraph 3.12 of the FAD, the Committee states:

“I*t recognised that there was a lack of detailed methodology on how to model carer utility. But it noted that the company used vignettes in the general population which was not in line with NICE’s Guide to the Methods of Technology Appraisal*”.

Paragraph 2.2.8 of NICE’s Guide to the Methods of Technology Appraisal confirms the requirement to measure health benefits that are important to patients and/or their carers. Paragraph 5.3.4 states how health-related quality of life should be measured:

“*The valuation of health-related quality of life measured in patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method*”.

While therefore, there is limited information in the Methods Guide in relation to the modelling of carer utilities, the approach followed by Kyowa Kirin (a choice based method, such as vignettes, applied in the general population) was in line with that directed at paragraph 5.3.4. In particular, contrary to the assertion in the FAD, the use of a method such as vignettes to generate carer utilities is positively recommended in the Methods Guide.

Finally, use of vignettes to generate carer utilities has been accepted in other appraisals, including:

TA614 Cannabidiol with clobazam for treating seizures associated with Dravet syndrome

TA615 Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome

HST11 Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations.

Therefore, rejection of vignettes to generate carer utilities on the basis that these are “not consistent with the Methods Guide” is incorrect and conflicts with the approach followed in other appraisals. This is procedurally unfair.

* 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**

Noted

* 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**

You suggest that this point of appeal should not proceed because, you say, the fact that the Committee has referred only to one factor listed in the Methods Guide at paragraph 6.3.3, does not mean that the Committee has omitted to consider the other listed factors. You consider that there was no requirement for the Committee to list all of the factors it took into account in the FAD, but only those it considered to be most important. You say that fundamentally a “*FAD is guidance to clinicians and it is reasonable that it focusses on matters of most importance to clinicians in a given appraisal, rather than, say, treating the list of factors set out in the methods guide as a checklist every element of which must be expressly discussed in a FAD, whether a significant driver of the decision or not*”.

Kyowa Kirin’s response

NICE is subject to a high level of procedural fairness and transparency in the conduct of technology appraisals. This is recognised in its procedures (see for example, the quotation from the Methods Guide at section 1.2 paragraph (a) above). It has also been confirmed by the Court of Appeal in R ota Eisai Limited v NICE[2008] EWCA Civ 438:

“*In conducting the appraisal process, NICE is discharging an important public function which engages a strong public interest. I have referred above to the vital role that NICE guidance has in determining the availability of treatments within the NHS - treatments which, as Mr Pannick submitted, may at the lowest have a substantial effect on quality of life and may at the highest save life. NICE has recognised this in its acceptance of the need for a very high degree of transparency in the process, with an exceptional degree of disclosure and consultation”*.

However, the issue in this point of appeal goes beyond transparency. Paragraph 6.3.3 of the Methods Guide states:

“*Above a most plausible ICER of £20,000 per QALY gained, judgments about the acceptability of a technology as an effective use of NHS resources will specifically take account of the following factors…*.”

Five factors are then listed, including “*uncertainty*” as well as “*whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured*” and “*the innovative nature of the technology”*.

Paragraph 6.3.4 of the Methods Guide proceeds:

“*As the ICER of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the Committee’s judgment about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed in section 6.3.3.*”

In this appraisal, the Committee has recognised: the impact of mycosis fungoides and Sézary syndrome on the health-related quality of life of carers, but decided that this should not be included in the economic modelling (paragraph 3.12 of the FAD) and the innovative nature of mogamulizumab (paragraph 3.17 of the FAD). However, there is no reference to these factors in the context of the Committee’s consideration of the appropriate ICER threshold. (It is Kyowa Kirin’s position that other factors, as listed in our Appeal Notice should also have been taken into account in this context, however for the purpose of this response, we limit our submission to the above two factors.)

There is accordingly no indication that the Committee has considered any factor other than uncertainty in its determination of the appropriate ICER threshold for the purposes of this appraisal, despite recognising elsewhere in the FAD, other factors listed as relevant in paragraph 6.3.3 of the Methods Guide. It is simply not valid to assume, in the absence of evidence, that the Committee has considered factors other than those listed or that it was in any way proper for the Committee to highlight only those factors listed in paragraph 6.3.3 it considered to be the most important. If the Committee’s reasoning omits certain of the listed factors, the only proper conclusion is that those factors have not been considered to be relevant by the Committee and have not been taken into account in its decision making. This is the general approach as a matter of procedural fairness, in the context of a requirement for reasons to support decisions made by NICE. However, the requirement is given particular force in the context of determination of the appropriate ICER threshold, by the specific obligation in paragraph 6.3.4 to make “*explicit reference to the relevant factors*” listed in paragraph 6.3.3.

In the above circumstances, the failure by the Committee to give consideration to factors listed in paragraph 6.3.3 which it has accepted elsewhere were relevant in the context of this appraisal is both procedurally unfair and inconsistent with the requirements of the Methods Guide.

* 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**

Noted

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

Noted

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

You express the preliminary view that the width of the ICER range in this appraisal does not, of itself, indicate procedural unfairness. You say that “*in many cases, there will be no single most plausible ICER, as different assumptions etc may be considered equally plausible*” and that “*these are points that have been considered by past appeal panels*”.

Kyowa Kirin’s response

The issue raised in this point of appeal is the lack of clarity surrounding the Committee’s preferred assumptions with the result that the most plausible ICER for the purpose of this appraisal is defined only by reference to a broad range. In particular, the Committee has failed to specify:

* Whether it prefers an analysis based on the HES data or the MAVORIC trial; and
* Whether it accepts adjustment of the data from the MAVORIC trial based on the IPCW methodology proposed by Kyowa Kirin or prefers the 2-stage estimation method.

While, in the context of an ultra-rare disease, there may be problems with all of the various approaches, the Committee should specify which of the options it views as preferrable for the purposes of calculating the most plausible ICER. In the absence of a clear decision, it is not possible for Kyowa Kirin to determine whether any commercial offer is feasible in order to ensure that a treatment, generally recognised as providing a substantial benefit to patients in the context of substantial clinical need, can be made available. However, based on the current wide ICER range and lack of clarity regarding the Committee’s conclusions, no such determination is possible. This is not in the interests of patients, clinicians, the NHS or Kyowa Kirin.

Finally, we have not understood your reference to points considered by past appeal panels as the relevant decisions are not identified in your letter. Therefore, if you are still not minded to allow this point of appeal to proceed to an oral hearing, we would ask you please to let us know to which appeal decisions your letter refers, so that we can consider these and provide our observations before you make your final decision.

* 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**

You suggest in your letter that the final sentence of paragraph 3.17 of the FAD is intended to convey the Committee’s view that the “relevant benefits” were in fact adequately captured in the assessment of cost effectiveness i.e. that the model was in a technical sense fit for purpose.

Furthermore, you say that you are not persuaded that the fact that the Committee has failed to reach any conclusion on the incorporation of carer utilities on the basis that all estimates are above the middle of the range normally considered to be cost effective, is a valid appeal point under Ground 1.

Kyowa Kirin’s response

We believe there may have been a misunderstanding in relation to the focus of this point of appeal. In particular, our appeal does not relate to whether the economic model is technically fit for purpose, but to the Committee’s assessment of whether the assumptions incorporated into the version of the model used for decision making, in fact captures all the relevant benefits of mogamulizumab therapy.

The issue in this point of appeal is therefore, that the Appraisal Committee applied the incorrect test. The question is not whether the relevant benefits “*could be*” captured in the model (the test applied by the Committee at paragraph 3.17 of the FAD) but whether they have actually been captured adequately, consistent with the assessment required at paragraph 6.3.3 of the Methods Guide:

“*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”* [emphasis added]*.*

The purpose of the analysis at paragraph 3.17 of the FAD is therefore to identify benefits which have not, in fact, been captured in the modelling. To the extent that such benefits have not been captured, this is likely to suggest that the calculated ICER is pessimistic.

You suggest that paragraph 3.17 conveys the Committee’s view that the relevant benefits were in fact adequately captured in the cost effectiveness assessment. However, that is not what paragraph 3.17 says and such a view would, in any event, be patently incorrect in the context of the Committee’s conclusions regarding the inclusion of, at least, carer burden and the effects of allogenic stem cell transplant in the economic model, both of which have been excluded, despite the Committee recognising that these are benefits of mogamulizumab therapy. In fact, the Committee simply approached the question incorrectly by reference to whether such benefits “*could be*” captured in the modelling rather than whether they had been captured.

The assessment by the Appraisal Committee at paragraph 3.17 of the FAD is therefore inconsistent with the Methods Guide and also conflicts with the approach taken by committees in all other appraisals of which Kyowa Kirin is aware.

Finally, you express the view that point (b), which relates to the failure by the Committee to reach any conclusion in relation to the impact of including carer utilities in the model on the basis that all cost effectiveness estimates were above the middle of the range normally considered to be cost effective, should not be permitted to proceed under Ground 1. Your reason is simply that “*[you] do not consider that procedural fairness requires a committee to provide this information*”. We respectfully disagree. The Methods Guide refers at several points to the requirement to take into account the position of carers including paragraph 2.2.8, which refers to the identification in the Scope of:

“… *the principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/or their carers*”.

If health outcomes relevant to carers are “relevant to the estimation of clinical effectiveness”, they must clearly be taken into account in the assessment by the Committee, otherwise the identification of such outcomes, as identified in the Methods Guide is futile. Furthermore, if they are taken into account, that assessment must plainly be communicated to stakeholders in accordance with basic principles of transparency and the standards referenced at section 1.2 paragraph (a) and section 1.5 above. Failure to communicate such assessments precludes any review of the conclusions reached and is inconsistent with rigorous decision making.

It is Kyowa Kirin’s position that the Committee should take into account all relevant health outcomes in the appraisal process irrespective of the ICERs calculated. However in this appraisal, the failure to consider the impact of carer burden is clearly procedurally unfair because the lower level of the ICER range is £33,000 per QALY gained, which is close to the range normally considered a cost effective use of NHS resources. In these circumstances, any impact resulting from the incorporation of carer utilities may make a material difference to whether the threshold is reached. If the Committee has not assessed the difference that including carer utilities makes to the ICER, it is clearly impossible for it to state with confidence that the result is still too high and if it has conducted an assessment then the results should be published as a matter of transparency.

1. **Ground 2**
   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**

Noted

* 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**

Noted.

We have addressed your proposal in relation to appeal point 1.2 in our response to that point above.

* 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**

You express the preliminary view that this point of appeal should not be permitted to proceed on the basis that:

(a) It is possible for reasonable people to reach different conclusions and the fact that the Committee did not adopt the opinions of the experts does not mean that they were acting unreasonably;

(b) You say that the fact that an analysis of time to next treatment (TTNT) from the MAVORIC trial was not mentioned in the FAD does not mean that it was disregarded; and

(c) You believe the company and the Committee have reached different but reasonable conclusions regarding the evidence of the patient expert.

Kyowa Kirin’s response

As explained at section 1.2 above, the choice of method for adjusting for patient crossover in the MAVORIC trial is of central importance to the outcome of this appraisal. The issue of the disease-modifying effect of mogamulizumab is one aspect of the Committee’s decision making in relation to the appropriate adjustment method and is therefore highly relevant to the outcome.

The issue raised by Kyowa Kirin in this point of appeal is that the balance of the evidence supports a probable disease-modifying effect of mogamulizumab:

* While the expert evidence identified at paragraph (a) is that mogamulizumab is disease-modifying, there is no expert evidence to the contrary to balance that view;
* Both TTNT analyses (showing longer TTNT from start of treatment as well as from start of subsequent treatments) from MAVORIC provides an indication of a disease-modifying effect;
* The patient expert opinion also indicates that symptoms do not return immediately after treatment is withdrawn, but return slowly, which is consistent with a disease-modifying effect of treatment and supported by the TTNT results on subsequent treatment seen in the MAVORIC trial.

This evidence is all consistent with a disease-modifying effect. While rejection of individual pieces of evidence might be justified as a difference of scientific opinion (in which case the conflicting opinion and evidence should be identified), it is the Committee’s refusal to accept the cumulative effect of all of this material that is unreasonable.

For completeness, if a reasoned decision fails to identify a piece of relevant evidence such as the TTNT analysis, then it must be assumed that the relevant evidence was not taken into account. In particular, there is clearly no basis for assuming that evidence which is not mentioned in the decision was in fact considered. To conclude otherwise would be to tip the balance overwhelmingly in favour of the decision maker and to deprive the requirement to provide reasons of any material effect, because it would be impossible: (a) for a person affected by a decision to know whether relevant factors had been considered; or (b) to exclude the possibility of *post hoc* reasoning being used to justify a decision. In other words, a decision must not only be reasoned, it must be adequately reasoned, and a decision maker may not rely on new reasoning developed after the event to justify its decision. In this case, there is no indication in the FAD that the TTNT analysis was taken into account and it must therefore be assumed it was disregarded, which is itself 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**

Noted

* 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**

Noted

Please let us know if further information or clarification would assist you. Alternatively, we look forward to receiving your final decision in relation to the admissibility of the appeal points raised in our Notice of Appeal.

Yours sincerely

XXXXX XXXXXXXX XXXXX

XXXXXX XXXXXX XXXXXXXX

Kyowa Kirin Ltd.

M: XXX X XXXXXXXXXX

E: XXXXXXXXXXXXXXXXXXXXXXXXXXXXX

1. [R (on the application of Clarke and Others) v Holliday [2019] EWHC 3596 (Admin)](https://www.bailii.org/ew/cases/EWHC/Admin/2019/3596.html) [↑](#footnote-ref-1)