Helen Knight
National Institute for Health and Care Excellence
Level 1A City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY EMAIL

12 August 2013

RE: Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID567]

Dear Helen,

Thank you for giving us the opportunity to comment on the ACD for the above appraisal; we have provided our comments under the standard four headings. Whilst we were disappointed that the Committee was unable to recommend MabThera (rituximab) in the draft guidance, we understand the complexity associated with the management of the disease and hope the information provided within this response will allow NICE to make rituximab available to a group of patients without alternative effective treatment options.

In developing our response we have once again sought the opinion of leading clinical experts who treat AAV in the UK. At the Committee meeting, there was a significant degree of uncertainty related to the standard clinical treatment pathway for patients with AAV; we note this was a key factor in the Committee being unable to determine the most likely ICER. We have since been able to gain clarification on the most appropriate treatment paradigm to model in our economic analysis.

[redacted]

Our economic model has been revised based on amendments suggested by the ERG and the Appraisal Committee. The updated base case ICER following all amendments is **£18,556/QALY gained**. All sensitivity analysis results have been updated and are tabled in this document.

ANCA-associated vasculitis is a rare condition with a paucity of randomised controlled trial evidence; however, there is significant experience in this area and strong clinical support for using rituximab in AAV. The overall likelihood that the ICER will be below £30,000 appears overwhelming; confirming that rituximab in AAV is a cost-effective use of NHS resources.

Yours Sincerely,

[redacted]

[redacted]

I. Has all of the relevant evidence been taken into account?

Following the Committee's request for further clarification and analyses, we have reviewed and updated the base economic model, conducted the requested sensitivity analyses, and sought clarification on the clinical management of AAV from clinical experts. We have outlined the requests from the Committee in the below table and the section where we have addressed each point.

Table 1: Contents of ACD Response

Committee's Request	Section
Definition of severe disease	5.3
Longer term data from RAVE	5.1
Retreatment with rituximab	2.3
Maximum cumulative cyclophosphamide dose	2.1
Definition of the subgroup for whom avoiding cyclophosphamide is desirable	3.2
Revised Economic Model	3
Changes suggested by the ERG	1.1;1.2
Discussion on relapse rates	2.5
Sensitivity Analysis on relapse rates	4
Costs and Disutility of long term cyclophosphamide use	4
Inpatient costs associated with non-remission (including treating infections)	4
Frequency of outpatient appointments for each health state	1.2
Scenario analysis showing the effect of azathioprine maintenance therapy	1.2; 4
Cost-effectiveness estimates for all appropriate treatment sequences	2.2;2.4;3
Cost-effectiveness estimates for all populations	3.1;3.2;Appendix
Pairwise and incremental analyses for the cost-effectiveness estimates	3

The following section provides a step by step guide to the updated analysis; we have separated the changes recommended by the ERG and accepted by the Committee and those changes recommended following further dialogue with clinical experts.

1. Revised Economic Assumptions based on ERG feedback

1.1. ***Recommended Changes by the ERG***

We accept that the minor technical changes proposed in the ACD section 3.42 by the ERG are fair, and therefore have been incorporated within our revised economic model.

Several other changes proposed in the ACD section 3.43 by the ERG were incorporated within our revised economic model:

- The assumed body surface area (BSA) and weight of patients was increased to better reflect patients within the UK. We have used the weight and BSA figures from a cohort of 30 vasculitis patients treated at the Manchester Royal Infirmary. The mean BSA is 1.90m^2 and the mean weight is 78.89kg.
- The model has factored wastage associated with drug delivery into the model.
- The utility value in the uncontrolled disease health state was adjusted from 0.671 to 0.71
- The cost of administering methylprednisolone was included in the model. It was assumed the cost would be equivalent to the cost of delivering rituximab (RTX) and CYC.
- The cost of an X-ray was updated to £18.56 and the cost of a CT scan was increased to £100. It was assumed that 80% of scans received in the modelled population would be X-rays, with 20% being CT scans.
- Relapse rates were estimated based on the data from patients who had severe flares after receiving CYC in RAVE to reflect the assumption only severe flares would lead to renewed induction treatment. The same relapse rate was applied to patients in the RTX group and patients in the CYC group. The relapse rate is assumed to be identical after subsequent lines of therapy.

1.2. ***Recommended Changes by the ERG not endorsed by the Appraisal Committee***

In the ACD section 4.16, the Committee disagreed with two assumptions within the ERG revised model. As a result, our economic model does not include maintenance therapy with azathioprine (AZA) following RTX therapy and we have updated the estimates related to outpatient attendance.

- As discussed at the Committee meeting, the use of azathioprine maintenance therapy following RTX is not supported by clinical evidence and as a result is not part of current UK clinical practice. The long term follow up from RAVE [Specks et al,2013], demonstrated that

the relapse rate between CYC and RTX was not significantly different. Patients in RAVE did not receive maintenance therapy with AZA unlike those in the CYC treatment arm.

- The frequency of outpatient visits assumed within the ERG model was not seen as accurately reflecting UK clinical practice. Experts at the meeting considered that the estimates may underrepresent the true cost of managing the disease. We have sought further advice on these estimates and have made only one change to the number of outpatient attendances (from 3 to 4 visits per cycle) in the uncontrolled disease health state.

Table 2: Outpatient attendances per cycle (6 months)

Health State	ERG Model	Revised Model
Non-Remission	13	13
Remission	2	2
Uncontrolled disease	3	**4**

2. Revised Clinical Assumptions following further clinical advice

We note that one of the major factors prohibiting the Committee making a decision on the most plausible ICER for RTX was uncertainty regarding the treatment pathway. We have sought clinical opinion from a number of experts who have provided a clear guideline on how severe ANCA-associated vasculitis is treated in the UK, and how RTX will be included in the treatment paradigm.

2.1. CYC maximum cumulative dose

We have sought to clarify the maximum CYC cumulative dose that patients would be exposed to in routine clinical practice. The assumed maximum cumulative dose directly impacts the number of assumed courses of CYC a patient is eligible for, and therefore plays a significant role in the economic model. It is well documented that an increased cumulative dose of CYC is correlated with an increased risk of malignancy [Heijl, et al 2011; Knight et al, 2004]. The risk of bladder cancer is reported to double for every 10 gram increment of CYC [Knight et al, 2004] reinforcing the preference for clinicians to minimise exposure where possible.

Clinical experts outlined that the maximum cumulative dose of CYC would depend on the availability of alternative agents for the treatment of severe disease. As a result clinical experts note that the total cumulative dose of CYC will differ between the standard of care treatment arm and the intervention arm which includes RTX (as noted in the ACD section 4.2).

In the UK, the maximum cumulative dose of CYC a patient would be exposed to would not exceed 25 grams or no more than two courses of IV pulse therapy. This is consistent with the recently drafted BSR guidelines [Watts et al, 2013] on the management on ANCA-associated vasculitis and with clinical experts we contacted. In our economic model, we have assumed patients in the standard of care arm will receive two courses of IV pulse therapy. This would equal approximately 23 grams of CYC based on the assumed weight of patients.

The revised model has assumed that all patients would receive IV pulse therapy. In our previous submission we had assumed a small proportion of patients (22%) would receive oral CYC. However, one 6 month course of oral CYC would equal the maximum cumulative dose of CYC. As the vast majority of clinicians use the IV pulse therapy regimen which is further supported in the recently drafted BSR guidelines [Watts et al, 2013], it seems appropriate that the model only considers IV pulse therapy as the comparator treatment. We note the ERG also outlined this approach would be more appropriate in section 3.35 of the ACD.

2.2. Treatment sequence

In our original submission we provided a number of analyses related to the assumed treatment sequence. Our revised analysis has been tested with a number of leading experts in the UK with significant experience in treating AAV with RTX.

In the RTX arm only one course of IV CYC would be administered before patient's transition on to RTX. This is further supported by the evidence in RAVE, where the pre-specified subgroup of patients with relapsing disease had a significantly improved remission rate to those treated with CYC induction therapy.

Under this approach a patient will not 'maximise' their lifetime cumulative dose of CYC, however, clinical experts have informed us that it would be very unlikely that a patient would be treated with CYC following RTX therapy. Clinical experts explained that using CYC following RTX is not supported by clinical evidence and would only happen in the rarest of circumstances.

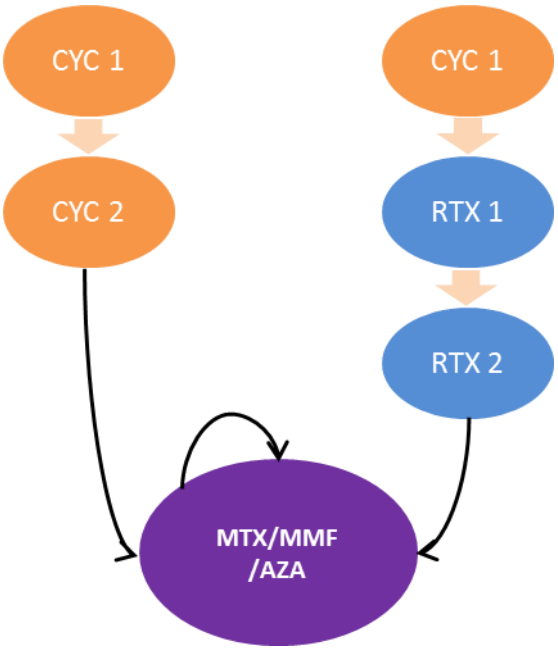
2.3. Retreatment with Rituximab

We have revisited the assumption surrounding retreatment with RTX. It was noted within the ACD that there was some uncertainty as to which patients would receive a second course of therapy based on the clinical experts contacted by the ERG. The clinical experts we contacted explained that all patients who relapsed following RTX would go on to receive an additional course of RTX.

Furthermore, the original model had arbitrarily diminished the complete remission rate for the second RTX course. We now have supporting evidence from the RAVE study where a small number of patients (n=16) received retreatment with RTX [Miloslavsky et al, 2013]. The complete remission rates for those patients retreated with RTX was 44% (n=7). We also note that there is additional evidence that demonstrates retreatment with RTX would generate high response rates similar to the first course of therapy [Jones et al 2009].

The diagram below outlines the treatment pathway presented in our revised analysis:

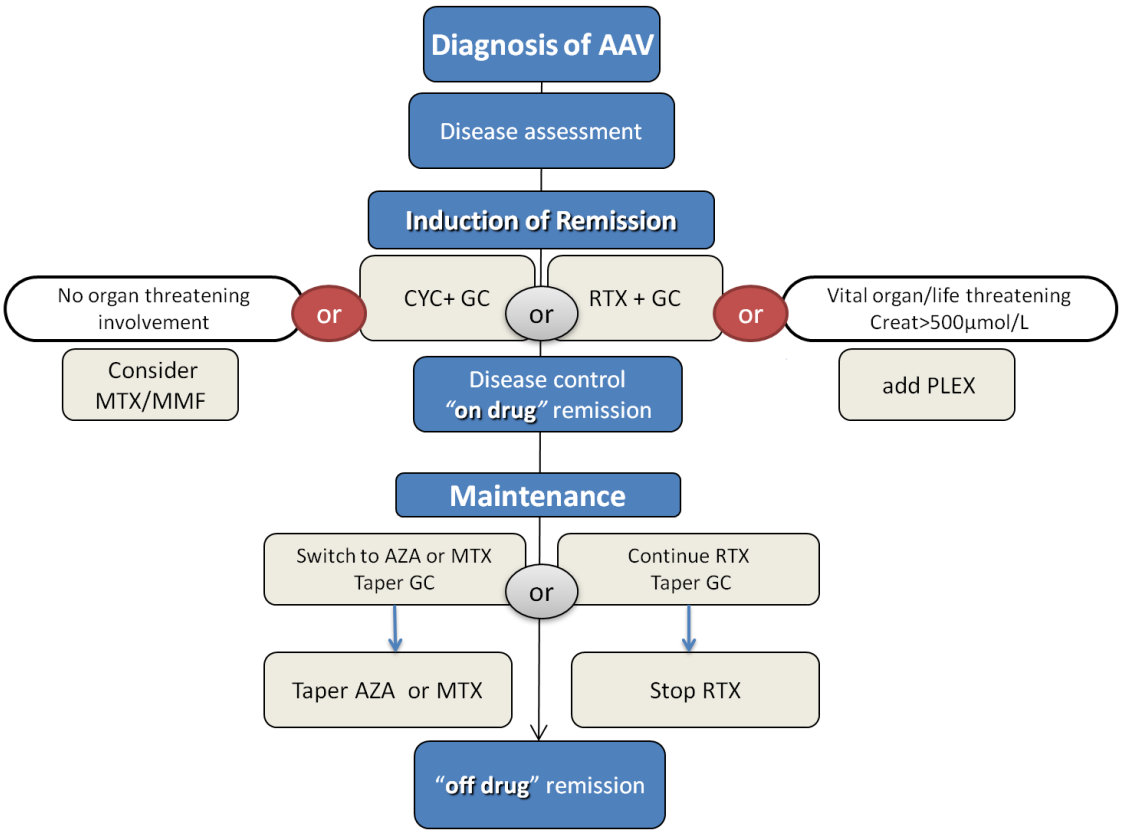
Figure 1: Treatment pathway for AAV patients



2.4. Relevant Comparators in the Base Case Analysis

The ACD outlines that our economic model has omitted relevant comparators, however at the Committee meeting, the clinical experts outlined that CYC was the only relevant comparator in the treatment of severe AAV (ACD section 4.1). The clinical expert highlighted in the meeting that alternative agents (methotrexate and mycophenolate) are generally reserved for milder forms of the disease. Although remission rates with methotrexate (MTX) and mycophenolate (MMF) for *de novo* patients are the same as for CYC at six months, relapse rates following either MTX or MMF are higher than CYC, and long term follow-up after MTX induction has revealed much higher glucocorticoid requirement and higher total CYC requirement [Faurschou et al, 2012]. Figure 2 below is the recommended treatment algorithm in the 2013 BSR guidelines [Watts et al, 2013]. This supports the use of CYC as the only relevant comparator in the base case analysis.

Figure 2: BSR treatment algorithm 2013



The Committee expressed concern regarding the plausibility of the uncontrolled disease health state (ACD section 4.13). The original model used a best supportive care cost as a surrogate for the cost patients would receive within this health state. We know that there are a number of alternative treatments that might be used where a patient relapses following induction therapy with either CYC or RTX. The revised model has assumed in the uncontrolled/active disease health state patients receive MMF, MTX, or AZA in line with their recommended dosage [Mukhtyar et al, 2009]. We have taken the average cost of the three therapies and applied this in the model. Furthermore, as discussed in section 1.2 of this response, patients will have on average four outpatient appointments per 6 months, based on further clinical expert advice.

As the clinical evidence for the use of MTX, MMF, and AZA in severe organ threatening AAV is extremely limited following induction therapy with RTX and CYC, we have assumed no difference in efficacy between treatment arms once patients enter the uncontrolled/active disease heath state in the model.

2.5. Treatment of relapses

Roche have had discussions with UK clinical expert nephrologists and rheumatologists, who are also leading experts in the treatment of vasculitis. Current clinical opinion is clear that systemic

vasculitis is, by definition, a severe disease. Some symptoms which may manifest on flare/relapse may appear minor but their potential for causing irreversible organ damage or death is major.

BSR guidelines indicate that for a minor relapse, steroids should be administered in the first instance [Watts et al, 2013]. Treating minor relapses with steroids may mask the symptoms for a period of time and may prevent further major relapse, but in some patients as soon as the steroids are reduced, the patient's vasculitis becomes unstable, leading to persistent, uncontrolled disease activity and irreversible organ damage.

Following discussion with clinical experts, we have therefore amended our assumption related to the treatment of relapse to align with the BSR treatment guidelines. The revised economic model assumes only major relapses will be treated with further induction therapy. While the exact proportions of patients requiring induction therapy following relapse may be difficult to determine (based on the role clinicians have in escalating a minor to a major relapse), it appears evident from the long term follow up in RAVE [Specks et al, 2013 Supplementary Appendix] that there is no difference between CYC and RTX in the rate of relapses (either minor or major).

The major relapse rate in the model is the same in the RTX and CYC treatment arm. The relapse rate is assumed to be identical after subsequent lines of therapy. This is consistent with the ERG assumption in their own exploratory analyses (ACD section 3.43).

3. Revised Cost-Effectiveness Analysis Results

In our original submission we provided cost-effectiveness estimates for the ITT population, the relapsing and newly diagnosed subgroups and an analysis in the small patient group who are intolerant to CYC. In section 1.2 of the ACD, the Committee asked Roche to also provide estimates for two additional subgroups, those patients for whom it is desirable to avoid CYC and those where CYC is inappropriate.

On further reflection Roche considers that the treatment populations can be separated into the following groups:

- Patients for whom CYC is an appropriate induction therapy (see section 3.1)
- Patients for whom CYC is not an appropriate treatment (see section 3.2)

The Committee requested incremental analyses be presented as part of our response. However, following the clinical advice we sought, we believe our base case treatment sequence best reflects actual clinical practice, therefore modelling the additional sequences would provide hypothetical results only.

3.1. Patients for whom CYC is an appropriate induction therapy

In the primary population where CYC is an appropriate induction therapy we had previously presented three separate analyses (all patients, relapsing, newly diagnosed). We now no longer consider it appropriate to present all three analyses considering the strong guidance from clinicians that they would use RTX only following CYC treatment; the Committee also heard from clinical experts at the appraisal meeting that this was the most appropriate treatment pathway to model (ACD section 4.2).

Presenting the cost-effectiveness of RTX in newly diagnosed patients, is not supported by clinical guidelines, therefore the result would appear to be theoretical, and not one that will reflect clinical practice in the NHS. We have provided the results to the all patients and newly diagnosed subgroup in the appendix of this document.

The revised base case analysis has incorporated the following changes:

- The changes recommended by the ERG listed in section 1.1 of this response.
- The amendments made to the ERG assumptions tabled in section 1.2 of this response

- Once patients enter the active/uncontrolled disease health state, they are assumed to receive treatment with alternative therapies MMF, MTX, and AZA. The costs and health outcomes are the same regardless of prior therapy.

The treatment pathway in the CYC eligible patient group is presented in Figure 1. The clinical inputs used within the model are presented in Table 3.

Table 3: CYC Eligible Patient Group Clinical Inputs

CYC			**RTX**		
Line of therapy	*Value*	*Source*	*Line of therapy*	*Value*	*Source*
CYC 1	0.6458	RAVE. CYC newly diagnosed subgroup	CYC 1	0.6458	RAVE. CYC newly diagnosed subgroup
CYC 2	0.420	RAVE. CYC relapsing subgroup	RTX 1	0.6667	RAVE. RTX relapsing subgroup
			RTX 2	0.4375	RAVE. RTX retreatment subgroup

As outlined in section 1.1 of this response, the relapse rate is consistent with the rate the ERG used within their exploratory analysis. This rate is based on the severe relapse rate in RAVE and is assumed to be the same in the RTX and CYC treatment arm. The relapse rate is assumed to be identical after subsequent lines of therapy.

Results - Patients for whom CYC is an appropriate induction therapy

In patients who can receive induction therapy with CYC for severe organ threatening ANCA-associated vasculitis, the ICER is estimated at **£18,556**. The table below provides further details.

Table 4: CYC Eligible Patient Group Revised Analysis

Treatment	**QALYs**	**Incr QALY**	**Total Costs**	**Incr Cost**	**ICER**
Rituximab	8.951	0.330	£27,821	£6,117	**£18,556**
Cyclophosphamide	8.622		£21,704		

Discussion

The revised economic analysis model demonstrates that RTX is a cost-effective use of NHS resources in the treatment of severe organ threatening AAV. Following the recommended changes outlined by the Committee, the model was adapted to reflect the most plausible treatment sequence. Expert clinical opinion and the new BSR treatment guidelines support the use of two courses of IV pulse therapy or where RTX is available, one course of CYC followed by RTX.

The model has used the complete remission rates from RAVE based on the appropriate line of therapy, demonstrating the most realistic patient pathway permitted using the evidence available. We note that an assumption on a similar relapse rate was made by the ERG which was supported by the Committee and is consistent with the long term evidence from RAVE [Specks et al, 2013].

Patients treated with RTX in the relapsing setting have a significantly improved complete remission rate leading to improved quality of life. This is reflected within the revised model design, leading to an incremental QALY gain for patients treated with RTX. The model has been unable to incorporate the long term health effects of high cumulative exposure to CYC which will be avoided in the RTX treatment arm by reducing lifetime CYC exposure. One could assume the model therefore underestimates the true benefit of adding RTX to the treatment pathway in the management of severe organ threatening AAV.

3.2. Subgroup analysis: Patients for whom CYC is not an appropriate induction therapy

The appraisal committee has requested revised cost-effectiveness estimates on three subgroups of patients for whom CYC is not an appropriate comparator treatment. While we recognise the groups are clinically different, they can ultimately be considered within one economic analysis where alternative therapies are used in place of CYC.

The Committee requested exploring the use of alternative induction agents for those patients who cannot receive induction therapy with CYC (ACD section 1.2). In the revised subgroup analysis patients are assumed to receive induction therapy with either MTX or MMF. In this section we will also outline the important clinical benefits that were omitted from this subgroup analysis that would have a significant effect on the cost-effectiveness result.

The Committee has described the subgroup of patients who cannot receive CYC induction therapy in the following three groups:

- Patients for whom it is desirable to avoid CYC
- Patients who are intolerant to CYC
- People for whom CYC is inappropriate

Expert clinical opinion estimates that collectively, the above three subgroups would represent less than 10% of all patients eligible for RTX therapy (as defined by having severe organ threatening AAV).

The current clinical definition for patients who cannot receive CYC, or for whom it is desirable to avoid CYC are detailed within the draft 2013 BSR guidelines and in the NHS Commissioning Board's recommendation for RTX in the treatment of AAV. We have additionally sought the opinion of experts to confirm that the following definition is in line with their own interpretation.

- *De novo* patients for whom CYC is indicated but in whom CYC avoidance is desirable

  (1) Fertility preservation in women

  (2) Patients at a higher risk of severe infection, tuberculosis, or chronic infection, such as bronchiectasis.

  (3) Uro-epithelial malignancy or dysplasia

  (4) Cytopaenia/bone marrow insufficiency

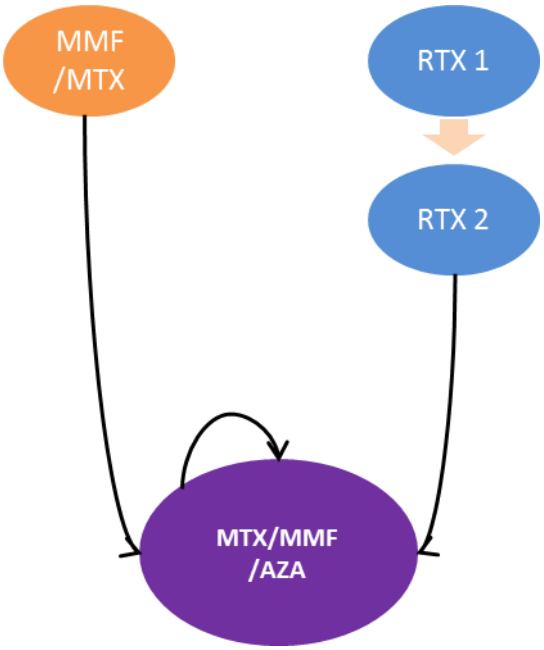
  (5) CYC allergy/intolerance

The revised economic analysis for patients for whom CYC is not an appropriate induction therapy has applied the following assumptions:

- The revisions outlined in section 1.1 and 1.2 have been incorporated within the revised analysis
- Patients in the standard of care arm are assumed to receive one 6 month course of either MMF or MTX
- MMF and MTX are assumed to have the same complete remission outcomes as CYC
- The 6-month probability of relapse rate for patients treated in the standard of care arm is 0.1031 compared to the relapse rate of 0.859 in the RTX arm. We have made this assumption in light of evidence noting the higher relapse rate of MMF and MTX compared with CYC in the induction of remission in severe AAV (see section 2.4 of this response). The relapse rate has been adjusted arbitrarily in the standard of care arm to be 5% higher than the relapse rate for CYC and RTX.
- Once patients enter the active/uncontrolled disease health state, they are assumed to receive treatment with alternative therapies MMF, MTX, and AZA. The costs and health outcomes are the same regardless of prior therapy.

The treatment pathway for the patient group for whom CYC is not an appropriate induction therapy is outlined in Figure 3.

Figure 3: Treatment pathway for AAV patients



Results - Patients for whom CYC is not an appropriate treatment

In patients for whom induction therapy with CYC for severe organ threatening ANCA-associated vasculitis is inappropriate, the ICER is estimated at **£35,003**. The table below provides further details.

Table 5: CYC Ineligible Patient Group Revised Analysis

Treatment	QALYs	Incr QALY	Total Costs	Incr Cost	ICER
Rituximab	8.624	0.2910	£28,667	£10,186	**£35,003**
MMF/MTX	8.333		£18,481		

Discussion

The small group of patients for whom CYC is not an appropriate induction therapy have the greatest unmet need in the absence of an effective alternative to CYC. Clinical guidelines strongly support the use of CYC to induce remission, other therapies such as MMF or MTX are not regarded as effective and are only recommended to treat patients with less severe AAV [Watts et al, 2013].

The ICER estimated in Table 5 is likely to represent **the upper bound** of the cost-effectiveness of RTX in patients for whom CYC is not an appropriate induction therapy. We note those patients wishing to have children currently face an extremely difficult trade off in managing their disease or choosing to preserve fertility. The effects of a patient becoming infertile have not been captured in

our analysis, but published evidence acknowledges the significant impact infertility has on a patient's mental wellbeing and their relationship with their partner [Hickman et al, 2011].

When considering the significant benefits that could be attributed to preserving fertility the ICER presented in Table 5 is likely to underestimate the cost-effectiveness of RTX in patients for whom CYC is not an appropriate induction therapy.

4. Sensitivity Analysis

We have undertaken the additional sensitivity analyses requested by the Committee on the following parameters within the base case:

- Relapse rates
  - Different severe relapse rates for CYC and RTX treatment arms
  - Assuming all relapses require induction therapy (major and minor)

Table 6: Sensitivity Analysis Relapse Rates

Assumption	Incr QALY	Incr Cost	ICER
Different severe relapse rates are applied (8.6% CYC; 10.8% RTX)	0.210	£7,304	**£34,775**
Assume an identical severe relapse of 10.8%	0.302	£6,815	**£22,559**
All relapses will require induction treatment	0.228	£7,960	**£34,942**

The choice of relapse rates on the model is a significant driver of the cost-effectiveness result. Clinical experts indicate that most minor relapses will be treated with steroids but those who experience a second minor relapse would be deemed as having a major/severe relapse based on clinical judgement. It therefore seems unlikely that the ICER related to all relapses being treated is clinically appropriate.

The most important driver is whether a difference in relapse rates between therapies is a clinically acceptable assumption. Considering the low patient numbers in these subgroups from RAVE, we consider that it may be more appropriate to apply the same relapse rate across treatment arms. This was supported by clinical evidence in the long term follow up in RAVE which showed no difference in relapse rates within these subgroups.

- Outpatient attendance frequency

When the outpatient attendances were set in line with the ERG reported values in Table 2, the ICER increased to **£21,170.**

- Maintenance therapy with AZA following RTX

The Committee requested a scenario analysis on the effect of maintenance therapy following RTX, however, as outlined in section 1.2 of this response, there is no clinical evidence supporting the use of AZA maintenance therapy. We have therefore not completed this analysis as it does not reflect clinical practice and is not supported by clinical evidence.

- Retreatment with RTX

As described in section 2.2, the treatment pathway involving RTX in the UK will involve two induction courses for patients with RTX. There is strong support for this approach, with clinicians sighting that almost all patients treated with RTX will respond [Jones et al, 2009; Specks et al, 2013] and therefore would be eligible for retreatment. We have tested two alternatives on who may receive RTX retreatment in Table 7.

Table 7: Sensitivity Analysis RTX Retreatment

Assumption	Incr QALY	Incr Cost	ICER
Only those who had a complete response	0.244	£4,538	**£18,564**
No retreatment	0.0682	£2,825	**£41,424**

- The wastage associated with RTX delivery.

Based on the revised average BSA of 1.9 (see section 1.1 of this response), the average dose of RTX is 712mg. The current model employs 100% wastage, which means one 500mg vial is used along with three 100mg vials. This is likely to overestimate the average cost per patient as no distribution has been applied to the BSA of patients from the Manchester clinic nor has consideration to the compounding of the treatment been included. Table 8 presents the results of the sensitivity analysis of the wastage associated with RTX.

Table 8: Sensitivity Analysis RTX Drug Delivery Wastage

RTX Wastage Assumption (mg)	Incr QALY	Incr Cost	ICER
88mg	0.330	£6,117	**£18,556**
40mg	0.330	£5,642	**£17,113**
0mg (no wastage)	0.330	£5,242	**£15,899**

When no wastage is assumed in the subgroup analysis for patients who cannot receive CYC, the ICER reduces to **£31,000.**

The following sensitivity analyses were also requested by the Committee:

- An analysis on the benefit for those patients looking to start a family with severe AAV

Unfortunately, we have not been able to undertake the above sensitivity analyses. There is supporting evidence on the impact that infertility can have on a patient's relationships and mental wellbeing [Hickman et al, 2011], however, due to the timelines we were unable to include this within out analyses of the subgroup of patients for whom CYC is not an appropriate induction therapy. However, it is evident that such an analysis should improve the cost-effectiveness results.

- Inpatient costs associated with treating infections from CYC treatment

Clinical experts at the appraisal meeting stated that CYC was associated with additional inpatient visits in some instances to treat serious adverse events, particularly infection. The increase costs and disutility associated with including this would improve the cost-effectiveness of RTX, however, we were unable to source the rates of inpatient visits associated with treating CYC adverse events.

- The costs and disutility associated with long-term toxicity from CYC

Clinical experts have explained that the introduction of RTX will reduce the long term burden of CYC exposure. The benefit of reducing CYC lifetime exposure will become more apparent in the coming years with long term follow up of patients using less CYC than the 25 grams recommended today, but as a result, we were not able to include this benefit within the economic model. This may result in an underestimation of the true cost-effectiveness of RTX in severe organ threatening AAV.

5. Further clinical data requested

5.1. New published long term data from the RAVE study

On the 1st of August the long term follow up to the RAVE study was published in the New England Journal of Medicine [Specks et al, 2013].

The publication highlights in particular, efficacy assessments at 6, 12 and 18 months for:

- Complete remission
- Duration of complete remission
- Complete remission for relapsing disease verse newly diagnosed disease
- Renal outcomes at 12 and 18 months

The supplementary appendix also highlights additional efficacy outcomes, including relapse rates, cumulative GCC dose, vasculitis damage index and SF-36.

The key long-term efficacy findings in RAVE out to 18 months were as follows:

- The proportions of patients who achieved complete remission (BVAS/WG of 0 on a prednisone dose of 0) at 6 months and who maintained complete remission at 12 months and 18 months were comparable in the RTX and CYC arms at 6, 12, and 18 months
- Rates of remission (BVAS/WG of 0) on a prednisone dose of < 10 mg/day were similar across treatment groups at 6, 12, and 18 months
- The mean BVAS/WG of each treatment group was similar at all-time points during the maintenance period
- The rates of remission were similar in both treatment groups despite a numerically lower cumulative steroid dose and lack of AZA maintenance therapy in the RTX group
- The rates of severe and limited flares did not differ significantly between treatment groups at 6, 12, and 18months; however, slightly more flares occurred after 6 months in the RTX than CYC group
- Overall, the findings between treatment groups were consistent across multiple efficacy endpoints at multiple time points

When adverse events were analysed on an intention-to-treat basis, there were no significant differences between the treatment groups in the numbers or rates of total adverse events, serious adverse events, or non–disease-related adverse events at 18 months. There was also no

significant between group difference in the number of participants who had at least one serious or non–disease-related adverse event. In total there were four deaths in the study, two in each group.

The authors concluded that no differences in overall adverse events were observed between the treatment groups, with the exception of fewer cases of leukopenia and pneumonia in the rituximab group.

The authors conclude that the efficacy outcomes in the rituximab group were consistently as good as those in the cyclophosphamide– azathioprine group over the course of 18 months, despite the fact that patients in the rituximab group who had a complete remission by 6 months received no additional immunosuppression for more than 1 year. “Thus, a single course of rituximab, at a dose of 375 mg per square meter once a week for 4 weeks, followed by placebo, was as effective in the treatment of severe ANCA-associated vasculitis as was conventional immunosuppressive therapy with cyclophosphamide and azathioprine administered for 18 months.”

Also, since the original submission, an abstract has been presented (but not yet published) at the Sixteenth International Vasculitis & ANCA Workshop, April 14-17, 2013, Paris, on a small number of patients (n=16) who had been retreated with rituximab in the RAVE study [Miloslavsky et al 2013].

5.2. Long term Safety

In section 4.8 of the ACD, the Committee considered that long term safety benefits of RTX had yet to be demonstrated, including the lack of effect on fertility and the reduced risk of malignancy compared with CYC.

We note there is supporting evidence for the long term safety of RTX in similar disease areas, notably Rheumatoid Arthritis (RA) where RTX is proven to be a well-tolerated safe treatment [Vollenhoven et al, 2013]. Van Vollenhoven and colleagues reviewed the long term safety of RTX from a global RA clinical trial programme which involved 3595 patients with over eleven years follow up (14,816 patient-years) and up to 20 courses of RTX. The paper concludes that RTX remained well tolerated over time and multiple courses and overall the findings indicate that there was no evidence of an increased safety risk or increased reporting rates of any types of adverse events with prolonged exposure to RTX during the 11 years of observation. The paper also concluded that there was no increased risk of malignancy observed.

In section 4.8 of the ACD, the Committee noted that there was uncertainty related to RTX’s effect on fertility. We have provided supporting evidence that demonstrates RTX, unlike CYC, does not prohibit patients from conceiving children [Pendergraft et al, 2013]. Pendergraft a colleagues undertook a retrospective audit of women in their clinic in the United States who were treated with

RTX for AAV. Out of the 157 woman treated, seven women wanted to have children, with 6 women successfully becoming pregnant (with a total of 8 pregnancies). Clinical experts strongly support the use of RTX in those patients wishing to conceive children.

5.3. Definition of Severe Disease

Within the supplement of the Specks et al paper, the definition of severe disease was clarified.

The designation “severe” ANCA-associated vasculitis applied in the RAVE trial was defined as disease activity that threatens the function of the affected organ and has the potential to induce irreversible organ damage or to threaten the patient’s life unless effective therapy is implemented promptly. Such disease manifestations include scleritis, peripheral or central nervous system involvement, alveolar haemorrhage, gastrointestinal involvement and glomerulonephritis.

This definition of severe disease formed the basis for the validated vasculitis disease activity assessment instrument BVAS/WG that was used in the Wegener’s Granulomatosis Etanercept Trial as well as the RAVE trial [Stone et al, 2001;TheWGETResearchGroup, 2005; Stone et al, 2010]. This definition of severe disease applied equally to patients with a new diagnosis or relapsing disease at baseline as well as to relapses occurring during the trial [Stone et al, 2010]. At inception of the trial, patients with one or more of these disease manifestations were considered to have severe disease that warranted treatment with the combination of glucocorticoids and cyclophosphamide as the standard of care. Patients fulfilling this definition of severe disease have been referred to by a variety of different terms including “generalized” [Jayne et al, 2003], “generalized organ-threatening” [Lapraik et al, 2007] or simply “organ-threatening” [Menahem et al, 2008] by other investigators, who all agreed at the time the RAVE trial began that such patients should receive glucocorticoids in combination with cyclophosphamide for remission induction.

II. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

The current summaries do not have all the evidence outlined in the above section; as a result we believe the current summaries are incomplete. We also note the below statement by the ERG which was clarified at the Appraisal meeting has been reported incorrectly within the ACD.

- In section 3.20, the ERG considered we had not adhered to the NICE Scope as a result of restricting our focus to the licensed indication.

As the Scope of the appraisal is limited by the licensed indications this is a factual error.

In section 4.18 of the ACD, the Committee states that it did not consider RTX to be a step change in the management of ANCA-associated vasculitis. A recent paper on the development of UK clinical recommendations for the use of rituximab in ANCA-associated vasculitis [Guerry et al, 2011] provided the following summation of the introduction of RTX in the management of ANCA-associated vasculitis;

"The introduction of CYC in the treatment of vasculitis 40 years ago was a major advance and its combination with glucocorticoids was the first reliable therapy that could achieve full disease control. Much of the clinical research in this area since has considered the toxicity of CYC and how this can best be managed by reducing exposure. To have an effective, safe alternative to CYC is, therefore, a major advance."

The Committee also conclude that there were no additional QALYs associated with RTX that had not been incorporated into the economic model. This is incorrect, due to the challenges in modelling the utility gain of a patient conceiving, we were unable to include this benefit within the model. For the subgroup analysis for patients for whom it is not appropriate to have CYC, there are QALYs which have not been included in the revised analysis presented.

The model does not associate any additional benefit on the avoidance of long-term malignancies which could be associated with high lifetime cumulative CYC doses. Since the introduction of CYC as a treatment for AAV, clinicians have been trying new ways of reducing the associated toxicities associated with its use. We know that the recommended lifetime cumulative dose of CYC has reduced from above 35 grams down to 25 grams. The introduction of RTX will allow clinicians to reduce further the maximum cumulative dose of CYC. While the benefits are hard to quantify, we know that even a reduction in the lifetime cumulative dose of CYC by 10 grams can half the risk of bladder cancer [Knight et al, 2004].

III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. As demonstrated in the original and subsequent analyses presented to NICE, rituximab in AAV is a cost-effective use of NHS resources.

IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

As highlighted above, a subgroup of patients with AAV may want to have children, however due to the infertility associated with the current treatment (cyclophosphamide), patients are forced to choose between improved disease control and having children.

While we have provided evidence on the infertility associated with cyclophosphamide, the real benefit of allowing patients to have children while effectively treating their disease cannot be captured within the context of an economic model.

Appendix

All Patients and Newly Diagnosed Results

In section 3.1 of this response we outlined the base case result for those patients who could receive CYC. The base case result used the complete remission rates for CYC and RTX based on the line of therapy it is assumed to be administered in, we know from clinical experts that RTX will only be used following CYC, therefore we consider using the results from the all patients and newly diagnosed subgroup may be not relevant, however for the purpose of completeness in addressing the Committee's requests, we have provided these results below. The results below have applied the same assumption as outlined in section 3.1 with the exception of the complete remission rates. Table 9 and

Table 10 provide the complete remission rates used within the all patients or newly diagnosed subgroup. The ICER for the ITT analysis is estimated to be **£19,655.** The ICER for the newly diagnosed subgroup is estimated to be **£21,207.**

Table 9: All Patients Analysis

CYC			**RTX**		
Line of therapy	*Value*	*Source*	*Line of therapy*	*Value*	*Source*
CYC 1	0.5306	RAVE ITT results	CYC 1	0.5306	RAVE ITT results
CYC 2	0.420	RAVE. CYC relapsing subgroup	RTX 1	0.6364	RAVE ITT results
			RTX 2	0.4375	RAVE. RTX retreatment subgroup

Table 10: Newly Diagnosed Analysis

CYC			**RTX**		
Line of therapy	*Value*	*Source*	*Line of therapy*	*Value*	*Source*
CYC 1	0.6458	RAVE newly diagnosed subgroup	CYC 1	0.6458	RAVE newly diagnosed subgroup
CYC 2	0.420	RAVE. CYC relapsing subgroup	RTX 1	0.6042	RAVE newly diagnosed subgroup
			RTX 2	0.4375	RAVE. RTX retreatment subgroup

Table 11: All Patients Analysis

Treatment	**QALYs**	**Incr QALY**	**Total Costs**	**Incr Cost**	**ICER**
Rituximab	8.885	0.339	£28,568	£6,473	**£19,655**
Cyclophosphamide	8.556		£22,095		

Table 12: Newly Diagnosed Subgroup Analysis

Treatment	**QALYs**	**Incr QALY**	**Total Costs**	**Incr Cost**	**ICER**

Rituximab	8.949	0.301	£28,091	£6,388	**£21,207**
Cyclophosphamide	8.622		£21,704		

References

Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Hoglund P, et al. Long-Term Outcome of a Randomized Clinical Trial Comparing Methotrexate to Cyclophosphamide for Remission Induction in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheum. 2012 Oct;64(10):3472-7.

Guerry MJ, Brogan P, Bruce I, D'Cruz D, Harper L, Luqmani R, et al. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2012 Apr;51(4):634-43.

Heijl C, Harper L, Flossmann O, Stücker I, Scott DG, Watts RA, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. Ann Rheum Dis. 2011 Aug;70(8):1415-21.

Hickman R, Gordan C. Causes and management of infertility in systemic lupus erythematosus. Rheumatology 2011;50:1551 1558.

Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert J, Dadoniene J, et al. A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies. N Engl J Med 2003;349:36-44.

Jones RB, Ferraro A, Chaudhry A, Brogan P, Salama A, et al. A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheum. 2009 Jul;60(7):2156-68.

Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 2004;63:1307–1311.

Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology 2007;46:1–11.

Menahem S, Hiremagalur B, Mudge D, Toussaint N, Walters G. Induction and maintenance therapy in ANCA-associated systemic vasculitis. NEPHROLOGY 2008; 13, S24–S36.

Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Retreatment with Rituximab in the RAVE Trial. The Sixtheenth International Vasculitis & ANCA Workshop, April 14-17, 2013, Paris.

Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–317.

Pendergraft W, McGrath M, Murphy A, Murphy P, Laliberte K, Greene M, et al. Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. Ann Rheum Dis 2013;0:1–2.

Specks U, Merkel P, Seo P, Spiera R, Langford C, Hoffman G, et al. Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. N Engl J Med. 2013 Aug 1;369(5):417-27

Stone J, Merkel P, Spiera R, Seo P, Langford C, Hoffman G, et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. N Engl J Med 2010;363:221-32.

Vollenhoven RF, Emery P, Bingham C, Fleischman R, Furst D, Hessey E, et al. Long-Term safety of Rituximab: Pooled Analysis of the Rheumatoid Arthritis Global Clinical Trial Program Over 11 Years. EULAR 2013

Watts R, et al. BSR Guidelines for the Management of adults with ANCA Associated Vasculitis. April 2013.

The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus Standard Therapy for Wegener's Granulomatosis. N Engl J Med 2005;352:351-61.