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BY EMAIL

25 April 2013

RE: Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID567] – Roche Response to Clarification Questions

Dear Helen,

Thank you for providing us the clarification questions for the above mentioned appraisal. In this document we provide written responses to all questions set out by the ERG and the NICE technical team. We appreciate the work that has gone into forming the questions; many of them reflect what we asked ourselves when developing the evidence submission.

Our economic model has been revised based on corrections suggested in ERG priority questions 32, 33, 34, 41 as well as low priority questions 42, 50, 51, 52, and 53. The updated base case ICER following all corrections is **£8,543.69/QALY gained**. All sensitivity analysis results have been updated and are tabled in the *Revised Economic Model* section of this document. We have summarised below our response to the major themes which arose within the clarification questions.

In developing our response we have again sought the advice of a UK clinical expert in AAV on the most appropriate comparator given the scope of the appraisal. The expert opinion we obtained has reaffirmed our assumption that cyclophosphamide (CYC) represents the standard of care for those patients with severe AAV who would be clinically suited to receive induction treatment with rituximab (RTX) in line with the RTX license. Although other regimens are used in inducing remission (methotrexate and mycophenolate), the clinical expert we consulted said that these treatments are reserved for patients with milder forms of AAV who are not eligible to receive RTX. Therefore, we would like to emphasise that we consider CYC to be not only the most relevant comparator agent in the appraisal, it is indeed the *only* relevant comparator agent.
We recognise the potential of the induction licence for RTX to cause confusion in respect of how best to assess cost-effectiveness. Under license, RTX should be restricted to the induction of remission in patients with newly diagnosed or relapsing AAV. RTX will not

be licensed as maintenance therapy even though, as the ERG noted, there is supporting evidence and furthermore strong clinical support for its use in settings outside induction. We sought clinical advice about which treatment sequences would best reflect how the induction licence will be implemented in clinical practice. These sequences are still assumptions, however, which is why we agree with ERG about the need to extensively test their impact in sensitivity analysis.

As we have stressed in the submission and this document, there is little evidence about how patients will actually respond/relapse within any of the treatment sequences we modelled, beyond the first course of treatment. The ERG suggests that we might have done more with outcomes data from the 'relapsed patients' subgroup from RAVE, potentially using it as a proxy measure of anticipated response/relapse when patients are re-challenged with either RTX or CYC. However, given the statistical power of this subgroup analysis and its unknown clinical relevance to re-treatment with RTX over a longer period, we continue to prefer an approach whereby response rates are adjusted in the sensitivity analysis. We are concerned that a scenario analysis based on RAVE sub-group point estimates may be unduly credited by an Appraisal Committee, because it came 'from the trial', when the actual clinical relevance is questionable at best and misleading at worst.

Please do let us know if you require any further clarification with respect to our evidence submission.

Kind regards,

[redacted]

[redacted]

Section 1: High Priority Questions and Requests

Literature searching

1) **Priority question:** Please clarify why only "RTX" is used as a search term for the intervention, rather than synonyms such as rituximab, Rituxan or Mabthera.

Roche note that Table 74 of the submission states "RTX" rather than rituximab or rituxan or MabThera. Roche reviewed the search strategy completed on 11/03/2013 and can confirm that the term "rituximab" was used.

2) **Priority question:** With reference to Appendix 1, please state whether searches for ongoing or completed and unpublished trials were undertaken and considered in the submission, using sources such as ClinicalTrials.gov, the metaRegister of controlled clinical trials, or the WHO ICTRP portal.

Searches for on-going or completed and unpublished trials were performed on ClinicalTrials.gov and the WHO ICTRP portal (search for rituximab OR Mabthera OR Rituxan AND vasculitis). Seventeen studies were identified. However, with the exception of RAVE and RITUXVAS, these studies were found to be either unpublished, not involving the licence population, not yet initiated, or, in one case, the study was withdrawn prior to enrolment. A complete list of studies is attached.

3) **Priority request:** The ERG believes that not all safety data have been retrieved from the direct evidence searches and that using the data presented in the Summary of Clinical Safety provided to the EMA is not sufficient. The ERG has provided search strategies for adverse events that could have been used in Appendix 1 of this letter. Please clarify whether there are any other relevant adverse event data that are not considered in the submission.

Roche believe that the safety information provided from the Regulatory Dossier, which includes data from RAVE, RITUXVAS and 12 other studies contains the data pertinent to inform the decision problem. However, Roche understand that the ERG may prefer to see data from a direct evidence search. Roche have performed a search exactly as outlined in the search strategy provided by the ERG in Appendix 1 of the clarification letter on 19/04/13 (in Embase, Embase alerts and Medline)and this has identified 2284 papers on rituximab and 8485 papers on CYC. Given the timelines, there is clearly not enough time to synthesise this amount of data and to ascertain how many of these are relevant to the decision problem. Roche have not had the time to extract and analyse these data, but are prepared to do so prior to the ACD meeting if requested by the ERG.

4) **Priority request:** The ERG believes that relevant comparators have been excluded from the manufacturer's submission due to the absence of direct evidence comparing them to rituximab. However, valuable evidence

comparing these interventions to cyclophosphamide (CYC) is likely to be available. Please clarify why searches that could have been used to inform indirect comparisons were not conducted. The ERG has provided a search strategy that could have been used in Appendix 2 of this letter.

The ERG is correct in that other comparators have been studied in the induction of remission in AAV. However, it is our understanding that the evidence base for these additional comparators does not reflect the population within the scope of this appraisal.

EUVAS conducted the pivotal trial of MTX vs CYC induction for non-severe disease (NORAM, de Groot et al 2007). It showed similar remission rates at 6 months, and more relapses after MTX at 18 months. A registry with 5-years of follow-up (Faurschou Arthritis Rheum 2011) showed higher relapse rates, much higher steroid exposure and higher overall CYC exposure in the MTX group at 5 years. UK expert opinion believes that this has reduced any enthusiasm for MTX induction. In addition, this does not reflect the scope of the analysis as RTX is to be licensed in severe AAV only, we therefore do not consider MTX an appropriate comparator in the analysis.

A study on mycophenolate mofetil vs CYC in a trial recruiting both severe and non-severe patients for induction of remission (MYCYC) has completed recruitment (EUVAS website), but we are not aware of any published results.

We believe that the most pertinent comparison to inform the decision problem is that of RTX vs the current standard of care (CYC) for induction of remission in patients with severe AAV. We note that, at the scoping workshop, clinical advice considered CYC to be the comparator for patients with severe CYC.

We therefore consider that, within the scope of the appraisal, CYC remains the relevant comparator.

Section A – Description of the technology, context, equality, innovation and the decision problem

5) **Priority request:** Please clarify why the oral regimen of CYC was used within the RAVE trial, and why that regimen has been used as the primary comparator in the submission. Some evidence suggests that 15mg/kg IV pulses have fewer adverse effects than oral 2mg/kg, while providing similar remission rates (de Groot, *Ann Intern Med*, 2009). This is particularly important given the cumulative lifetime dose limit associated with CYC – the IV regimen is very likely to lead to a lower dose of CYC received per cycle, which may enable a larger number of cycles to be administered over time for an individual patient.

The RAVE study did not involve any UK centres. We agree that in the context of UK clinical practice, IV pulse therapy may represent an alternative standard of care for patients with severe AAV. The RAVE study was designed in accordance with advice from the USA Food and Drug Administration (FDA). Since no other treatments are

licensed for the treatment of AAV, the choice of comparator will vary based on clinician and patient preference.

Whilst some clinical evidence supports the use of IV CYC over oral CYC, we note that the efficacy of IV and oral are generally accepted to be very similar. Our economic model has assumed that a proportion of patients will receive IV pulse therapy (the proportion being informed by a market research survey we carried out). Our model captures the increased costs associated with the delivery of IV pulse therapy. We have assumed that the safety profiles of oral and IV pulse CYC do not differ, and for that reason the AE rates for both routes of administration are based on the RAVE study results. We have tested the impact of these assumptions through a scenario analysis which are presented in question 13.

6) **Priority request:** With respect to Section 5, statements made and supported with the rationale that they are "*in line with the proposed licence*" are inadequate given later, possibly equivocal statements such as 6.9.2: "*The RTX licence is likely to cover the induction of remission*".

- Please clarify by specifying and defining each element of the proposed licence. The ERG notes that the EMA CHMP positive opinion does not specify whether rituximab should only be used in newly diagnosed patients.

The license population is not restricted based on any prior exposure, treatment failure or contraindication related to CYC.

- Please include clarification on whether the population is limited to those contraindicated for, or refractory to CYC.

No the population is not restricted based on prior contraindication to CYC.

- Also please clarify whether the only possible intervention regimen is 375mg/m² x4, for induction for *de novo* disease only (1st line) for the stated populations, or for induction after first relapse (2nd line) after CYC only.

The licence dose within the SPC will state that for all patients the recommended dose is 375mg/m² x4. In the Decision Problem table, we said that a number of UK clinical experts currently choose to use the 1g dose (typically used for the treatment of rheumatoid arthritis). We have not examined the impact of using this dose as it falls outside the license and is not something we could legally promote.

7) **Priority question:** Given that the RAVE trial looked at the use of RTX to treat flares, why will this not be included in the licence?

The licence for RTX will cover the treatment of severe AAV (Granulomatosis with polyangiitis GPA, and Microscopic polyangiitis MPA) as a treatment for induction therapy. We note that this will cover all patients regardless of prior therapy, as the pivotal study RAVE included both newly diagnosed and relapsing patients.

The effect of retreatment with RTX was not a primary aim of the RAVE study. Since completing our submission we have been made aware a small number of patients were followed who received retreatment with RTX (n=15). This evidence was published in April in abstract form only. We have provided the abstract relating to the retreatment of the small number of patients in the RAVE study.

8) **Priority question:** Given that maintenance therapy with RTX appears to be used in practice, and has been included in various studies, why will this not be included in the licence?

The CHMP and EMA decided to exclude maintenance therapy from the Marketing Authorisation. Our regulatory submission to EMA did include evidence supporting the use of RTX in maintenance, but ultimately the EMA found this evidence insufficient. We were disappointed by the decision as we have seen strong support from clinical experts for its use in this setting. Furthermore, we note that the FDA did not restrict the US license, allowing its use in both induction and maintenance.

In December 2012, the NHS Commissioning Board published draft guidance recommending RTX for the treatment of AAV in a much broader setting than approved by EMA. The NHS commissioning board has specifically recommended RTX as a 'remission maintenance agent'. We are also aware there are UK studies evaluating the effectiveness of RTX maintenance therapy [Smith RM, et al 2012].

Section B – Clinical Effectiveness

9) **Priority request:** With respect to Section 6.2.7, please clarify the justification for including each of the non-RCT studies as supporting evidence. In Section 6.7.1 it is stated that the non-RCTs were "*found not to have sufficient data to be useful to the decision problem*". Please clarify this statement providing justifications. Currently, it is not clear how or why these trials could not contribute to the decision problem, especially as some are cited later in 6.8.1 as having relevant safety data. A clear justification also needs to be given for not appraising these trials critically.

Roche agree with the ERG that the addition of the non-RCTs to section 6.2.7 and then the exclusion of the same studies in section 6.7.1 may be potentially confusing. Furthermore, the lists in the two sections are not identical, due to an editorial error.

However, the non-RCTs were added in section 6.2.7 to concord with the STA template and to be fully transparent (7 non-RCTs were identified as part of the systematic literature search). Although the 7 non-RCTs fulfilled the inclusion criteria for the search, they were found not to have sufficient data to be useful to the decision problem. The reasons for their non-inclusion are described in the attached table.

As the papers were found not to contain sufficient on-label data to contribute to discussion of the decision problem, they were not subjected to a full critical appraisal.

10) **Priority request:** In Table 9 it is stated that patients with a serum creatinine level of >4.0 mg/dL were excluded from the RAVE trial. Please clarify that the RAVE population therefore does not include patients with severe renal disease.

The ERG are correct in stating that patients with a SCr >4.0 were excluded from RAVE. They were excluded because it was likely that they might require plasma exchange which would be confounding for both efficacy and safety, and also that plasma exchange may affect the PK of rituximab based on the timing of exchanges and dosing.

The definition of “severe renal disease” is problematic because patients with GPA or MPA and renal involvement are at risk for a diagnosis of Rapidly Progressive Glomerulonephritis (which is predictive of development of ESRD) yet may still have a serum creatinine (SCr) <4.0 at a specific time-point. “Severe” may be best defined as organ or life threatening activity that would be considered to require CYC or an alternative agent. A patient whose SCr increased from 0.8mg/dl to 3.2mg/dl would be considered to have lost the majority of their renal function yet would still fall below the SCr 4.0 cut-off.

The RAVE cohort did not generally include patients with severe renal disease that would require dialysis or plasma exchange at the time of randomization. This is in contrast to the RITUXVAS trial. In RAVE, fifty-two percent (102/197) of the patients had major renal disease at entry which was defined by the presence of a pauci-immune glomerulonephritis (GN) on renal biopsy and/or presence of at least one major renal item on the BVAS/WG score. Major renal items included RBC casts on urinalysis and a greater than 30% rise in serum creatinine or >25% decline in creatinine clearance. Fifty-one patients with major renal items were randomized to RTX and 51 to CYC/AZA,and the mean baseline e-CrCl was lower in the RTX group (54 ml/min vs 71 ml/min p=0.01).

11) **Priority question:** With regard to Section 6.3.6, please clarify and justify more fully the choice of the 70% rate of 6-month remission in this population (treated with CYC) based on WGET trial 2005 (n=180), given that de Groot, *Ann Intern Med*, 2009 (n=149) = 87% at 9 months; Jayne, *NEJM*, 2003 (n=155) = 93% at

6 months, and RITUXVAS = 82%, sustained, at 12 months; all report higher rates for CYC in *de novo* AAV populations.

The 70% CYC treated expected remission rate was the most recent reliable data from a RCT including both newly diagnosed and relapsing patients available at the time of trial planning. While remission definitions tend to have uniformity across trials (BVAS=0 or BVAS/WG=0), there is considerable variability in the background prednisone dose allowed at the time of the endpoint, and also in the timing of the endpoint. Allowance of prednisone use will increase remission rates, albeit with the expected increase in steroid related side-effects.

Longer durations of follow-up would also be expected to increase remission rates among patients that have achieved a significant response early in treatment; the RAVE data are consistent with this premise.

In CYCAZAREM (NEJM 2003), the patient population was different in that a higher proportion had renal involvement and MPA.

12) **Priority request:** The choice of subgroup analyses presented in Section 6.3.7 needs to be clarified, justified and described, as required: "*specify the rationale and whether they were pre-planned or post-hoc*". The RAVE trial describes a series of analyses as "*predefined*", but the ERG cannot see these described in the article itself, the freely-available clinicaltrials.gov protocol (NCT00104299) or the NEJM accessible, supplementary file protocol. Please clarify where these subgroup analyses were pre-specified. This is important as *post hoc* sub-group analysis was a stated exclusion criterion in Section 6.2.

These subgroups were pre-specified and listed in the Statistical Analysis Plan which was generated by the trial sponsor and submitted prior to database lock and reporting of the primary efficacy results. An extract from the SAP is outlined below.

From the SAP: Examination of Subgroups
The effects of various baseline characteristics were explored in relation to outcome with either treatment. Subset analyses of the primary endpoint were conducted using pre-specified prognostic factors such as new vs. relapsing disease, type of ANCA (PR3+ or MPO+), serum creatinine, and age.

The consistency of the primary endpoint results was explored, in an ad hoc fashion, within study centres, and within subgroups defined by demographic or baseline disease factors such as gender, AAV type (WG or MPA), renal involvement (yes/no), alveolar hemorrhage (yes/no), creatinine clearance (< 60 mL/min or ≥ 60 mL/min), and systemic disease (yes/no).

13) **Priority question:** No indirect comparisons were drawn in the manufacturer's submission. However, several comparator interventions included in the scope

for this appraisal have been excluded. Also, the RAVE trial includes oral CYC as the comparator, whereas the ERG's clinical advisors suggest that IV CYC may provide a better safety profile, and results in a lower cumulative dose of CYC per cycle. While there may not be direct evidence on all potential comparator treatments, there is likely to be indirect evidence (comparisons to CYC / IV CYC) in a number of cases. The ERG's clinical advisors suggest that other treatments are likely to have an important role to play in the treatment of ANCA-associated vasculitis, as part of treatment sequences. Please clarify why indirect comparisons were not undertaken for both efficacy and adverse events.

As set out in more detail under question 22, we do not believe that relevant comparators have been omitted from our economic analysis. For patients eligible to receive RTX induction, the clinical expert advice we have received states unequivocally that CYC induction is the only relevant comparator.

There remains considerable variance in practice about the use of oral vs IV pulse CYC, and the decision was made to use oral CYC in RAVE based on experience in the CYCAZAREM and WGET trials, and the prior extensive literature on oral CYC prior to CYCLOPS.

Whilst the model uses AE rates from RAVE, a large majority of patients in our model are actually assumed to receive IV CYC rather than oral. This means that the IV mode of administration is accounted for in terms of cost but not in terms of any potential AE benefits.

We believe that running an indirect comparison of studies which measured efficacy and AEs in IV and oral CYC and then building its results into our economic model is unjustified given the limited amount of evidence available.

We have undertaken sensitivity analysis on the AE rates associated with CYC to explore how this this assumption may have affected the ICER. The results are presented below.

	AE QALYs		
	Base Case	**Tested Value**	**Tested Value 2**
RTX	-0.0302	-0.0302	-0.0302
CYC/AZA	-0.0333	-0.0302	-0.0250
Incr AE	0.0032	0	-0.0052
ICER	£8,543.69	£8,713.78	£8,823.17

14) **Priority request:** Please clarify exactly how the safety studies in Table 33 were sourced and the inclusion criteria that were applied; please clarify the reason for the omission of potentially relevant non-RCT evidence from this list

(e.g. the non-RCT studies by Holle, *Ann Rheum Dis*, 2012, Roll, *J Rheumatol*, 2012 and Cartin-Ceba, *Arth Rheum*, 2012; all use a 375mg/m² dose of RTX and report safety outcomes).

The safety studies were sourced prior to 2010 for inclusion in the sBLA submission in the US and the subsequent EMA dossier application in 2011. The EU dossier for AAV was based on the US dossier. The US approval had already been granted by the time of the EU filing, and the Roche interpretation of the data had not changed between time of the US approval and the EU filing.

As there was no requirement by the FDA or EMA to show the methodology for literature searches supporting US or EU Regulatory filings, this was therefore never formally captured and Roche are unable to provide this at this time. Roche are willing to review the search results in order to comply with the NICE search strategies, though we consider the most relevant evidence has already been captured within our submission.

15) **Priority request:** In Section 6.8.2, only safety data from RAVE and RITUXVAS are actually considered. Please clarify why this is and why data from the other studies cited in Table 33 are omitted.

The ERG is correct in stating that the evidence on safety pertaining to the decision problem related mainly to the safety data arising from RAVE and RITUXVAS.

A small amount of additional safety information was provided from a number of smaller published investigator-initiated studies in which a total of 162 patients had been treated with rituximab for AAV (Table 33 in the original submission). As data from these studies were from the published literature, information was very limited and it was therefore more problematic to draw robust conclusions.

This group of studies comprised uncontrolled case series of patients who had failed or were intolerant of standard therapy or who had relapsing disease. Patient populations were variable across these studies. Whilst the dose of rituximab administered was generally consistent (375 mg/m^2 weekly ≥4), therapies given concomitantly with rituximab varied (Table 33 in the original submission). The duration of follow up for safety, as well as the type and amount of safety data reported, also differed across studies.

16) **Priority request:** Please provide tables presenting adverse event data for each grade 3 or above event observed in each treatment arm in RAVE and RITUXVAS. For RAVE please present data for 6 month and 18 month timepoints. Data may be provided in a similar form to Table 40 (but with the inclusion of the number of patients with the event, the number in the group, and the percentage with the event).

Roche is not entirely clear on the data cut that the ERG have requested; there are no tables available that list each AE Grade ≥ 3 event individually by treatment at the specified time points. However, Roche have attached tables of overall safety summary showing the numbers and percentages of patients with AE Grade 3, 4 and 5 at 6 and 18 months for RAVE and AEs Grade ≥ 3 at 12 months for RITUXVAS.

Section C – Economic evaluation

17) **Priority question:** It is stated in Section 2.5 that only major relapses lead to treatment with CYC. In the model do the relapses represent major relapses based upon the RAVE trial, or are mild / moderate relapses also included? Or are all relapses included and assumed to be major?

Our economic model defines all relapses as necessitating treatment with CYC or RTX (depending on which arm patients are in). We chose to use this assumption because, although in reality patient progression in AAV is a complicated path with a variety of events possible, our main trial does not capture this complexity. We felt it was more appropriate to develop a simple model whose parameters can be varied in sensitivity analysis.

The clinical expert we consulted said that with close monitoring, most relapses are identified while they are still mild, and if left untreated most of these will subsequently develop into major relapses. This means that in clinical practice, although some patients experiencing a minor relapse may just have their steroid dose increased, almost all will ultimately have a more serious relapse justifying treatment (or retreatment) with CYC/RTX.

Our clinical expert considers retreatment with CYC or RTX at the first sign of relapse. For example, if patient relapses whilst on CYC, treatment with RTX would be considered immediately to avoid irreversible harm potentially caused by waiting for the relapse to develop into a major one.

Our economic model has not modelled different categories of relapse. Instead we assume that the majority of relapses will lead to retreatment with CYC or RTX (depending on arm). We acknowledge that some patients may not require retreatment with CYC or RTX immediately, but as we have no way of determining which minor relapses might eventually progress to major ones, nor what time scale such progression might happen on, we have not factored this distinction into our analysis.

We note that similar simplification has been assumed in the modelling of rheumatoid arthritis drugs. Here, patients who fail to achieve a treatment response (ACR response) are assumed to move on to the next line of therapy. Due to evidence constraints no consideration is given as to whether their disease remains severe (as categorised by a DAS28 score >5.1).

18) **Priority question:** Please clarify why relapses of different severity were not modelled.

Please see the response above.

19) **Priority question:** Stone *et al* 2010 is given as the source for the relapse rates presented in Table 44, however the ERG cannot find these figures in the paper. The ERG understands that these rates were calculated by fitting exponential models to time-to-relapse data from RAVE. Measures of explained variation such as R^2 are not recommended for use with time-to-event data (Collett, 2003).

- Please provide relevant data on the fit of the exponential models (such as AIC and BIC statistics) compared with alternative parametric models.
- Please clarify whether proportional hazards were assumed and justify the use of exponential models rather than other parametric models.
- In graphs such as that presented in Figure 14 please include values for numbers at risk.

We are unable to provide the AIC and BIC statistics as patient level data was not used in estimating the relapse rates for patients in the model. We applied the exponential to the summary statistics from the RAVE study in order to estimate a constant rate of relapse in the model for both treatment arms. The source given for the relapse rates is incorrect; the correct source for table 44 is: RAVE CSR: 120 day safety update, page 105, figure 4.

20) **Priority question:** Please explain the relapse rates presented in Table 38.

- Were these calculated using exponential models fitted to the subgroup data from RAVE?

Exponential models were fitted to the subgroup data from the RAVE study. As noted in question 19, patient level data available in calculating the relapse rates in the model.

- It seems surprising that “newly diagnosed” and “relapsing patients” relapse rates of 0.07 and 0.17 respectively for CYC combine to give a relapse rate of 0.15 for all patients; whereas rates of 0.12 and 0.31 respectively combine to 0.16 for RTX. Is this due to the fit of the exponential models?

The fit from the exponential curves was based on summary statistics, not patient level data. This, as well as the low patient numbers in each arm (n=49),

led to less precise estimates for relapse rates in subgroups. In particular, we note a counterintuitive result in the “relapsing patients” group (i.e. patients who previously received and relapsed on CYC). Specifically, the RTX arm was associated with high rates of relapse compared to the CYC arm; we would have expected the reverse to be true. Within our original submission we highlighted that the subgroup results should be interpreted with a degree of caution due to the low patient numbers (Section 7.7.10).

- Please provide the information specified in question 20 for these subgroup analyses.

The source for the relapse rates can be found in the attached *RAVE data on file*. The relapse rates can be found in 9.6.1.1 and 9.6.1.2 for relapsing and newly diagnosed disease.

21) **Priority question:** The economic model looks at a situation whereby RTX may be used as a remission induction agent in newly diagnosed patients and in previously relapsing patients. However, the model does not consider a sequence whereby newly diagnosed patients initially receive CYC and following relapse they receive RTX. Please clarify why this sequence is not considered.

The impact of this sequence is covered in our sensitivity analysis of the “relapsing patients” population in Table 69 of our submission. That analysis used efficacy data from the subgroup of RAVE patients who had previously received - and relapsed on – CYC. The analysis also set up the model such that patients do not receive any further CYC.

Our model has been designed to assess the cost-effectiveness of RTX as an induction agent in the treatment of severe AAV. In consideration of the available evidence and appraisal scope, the possible treatment sequences modelled in our sensitivity analyses are sufficient to inform discussions about treatment sequences which may arise within the boundaries of the Decision Problem.

22) **Priority question:** Please clarify why a wider range of possible treatment sequences were not considered in the economic analysis. The ERG’s clinical advisors suggest that treatments other than rituximab and CYC may play an important part in the treatment pathway for ANCA-associated vasculitis. This is linked to question 22, as regards the positioning of rituximab within the pathway, but also involves the consideration of additional treatments within the pathway.

The clinical advice we received outlined clearly that for patients to be considered for RTX, the only relevant comparator technology is CYC. The clinician we spoke with said that whilst patients with milder forms of AAV may receive mycophenolate or methotrexate, these patients are generally not considered to be candidates for RTX and indeed do not fall within the scope of this appraisal.

The NORAM study [de Groot et al 2007] evaluated MTX against CYC induction for non-severe disease. Although remission rates were similar at 6 months there were significantly more relapses at 18 months in the MTX arm; since publication of this study, we are told, MTX is no longer regarded as the standard of care for inducing remission in AAV.

As noted in question 17, we have assumed all relapses to be major and necessitating immediate retreatment with CYC or RTX. We did this to reflect a clinical opinion that regardless of the initial relapse severity, patients will later progress to a major relapse and will receive CYC or RTX.

23) **Priority question:** Please clarify why the base case version of the economic model allows newly diagnosed patients to only receive 2 courses of CYC once they enter the model, whereas previously treated patients are also allowed to receive 2 courses of CYC once they enter the model.

Our rationale for the number of CYC cycles offered was based on expert opinion. We have however addressed this point within the sensitivity analysis in Table 69. When this assumption was tested (i.e. patients with relapsing disease assumed to receive no further courses of CYC) the ICER estimated at £12,556.29.

24) **Priority question:** Please clarify the rationale for assuming that all patients that initially do not respond to rituximab treatment are immediately retreated with rituximab. Clinical experts consulted by the ERG suggest that this assumption is questionable.

We fully acknowledge the uncertainty regarding the retreatment of patients with RTX. We believe there is little clinical consensus on how RTX should be used within the proposed licence. Some clinical experts may not recommend waiting until relapse for retreatment and would choose maintenance therapy to improve clinical outcomes. We note that a number of centres are currently administering RTX as a maintenance therapy which is supported by the NHS Commissioning Boards draft recommendation for RTX in AAV. We note that the use of RTX maintenance therapy falls outside the license and therefore scope of this appraisal.

We have tested which patients are eligible for a second course of RTX in the sensitivity analysis of the model. The results in Table 68 are presented below.

Table 1: Which patients are offered a second course of RTX

Tested Variable	ICER
Non-remitters	£8,543.69
Relapsing patients only	£9,502.83
No patients	£7,197.34
All patients	£9,663.61

25) **Priority question:** Please provide further clarity and justification around the assumption that following relapse after initial treatment with rituximab, one course of CYC will be given.

We found little evidence about how many cycles of CYC an average patient would receive following RTX. We believe that our base case assumption (one course of CYC only following RTX) is conservative because the patient's opportunities to benefit are limited. In the absence of better evidence, we varied the number of CYC courses in sensitivity analyses. The results in Table 68 of our submission show all but one scenario to be cost-effective. The one scenario which had an ICER for rituximab in excess of £30,000/QALY gained was where patients receiving RTX are offered no further treatment. We consider this scenario unlikely given the prominence of CYC in the management of AAV.

26) **Priority question:** Please justify why it is reasonable to assume that the probability of obtaining remission with CYC is the same (that is, it is equal to that observed for "all patients" in the RAVE trial, rather than that observed for "relapsing patients") regardless of prior RTX therapy.

There is evidence to support the diminishing returns associated with repeat courses of CYC. We are not aware of evidence to support a diminished rate of response for CYC following RTX. It would appear from the literature [Hoffman et al, 1992] that it is the repeated use of the same agent that reduces the subsequent cycles' effectiveness. Therefore, with the absence of any evidence we have assumed that following the four week course of RTX patients who previously relapsed on CYC have the same average probability of achieving remission as the whole-patient group in RAVE.

27) **Priority request:** Please clarify why sensitivity analysis was not undertaken around the assumption that the diminishing effectiveness associated with a second rituximab course is the same as the diminishing effectiveness observed between the CYC newly diagnosed and relapsing patient groups

In Table 67 we have presented sensitivity analysis on a number of parameters. We have tested assumptions related to the diminishing returns associated with subsequent cycles of RTX. The result was not overly sensitive when the diminishing effectiveness assumption was removed in both CYC and RTX arms.

28) **Priority question:** Please clarify the implications for the economic model of basing the CYC efficacy and adverse event data on the RAVE trial, in which

CYC was administered orally. The ERG's clinical advisors suggest that IV CYC is likely to result in fewer AEs, and also a lower dose of CYC per cycle, which may allow more than 2 cycles of CYC to be given.

Our economic model may overstate the AEs associated with CYC as this was based of the RAVE study where CYC was only administered orally. We have undertaken an additional scenario analysis where the adverse event rates have been reduced, to test the effect on the ICER, the results are presented in question 13.

The clinical advice we received relating to the number of CYC cycles was in respect to IV pulse therapy.

29) **Priority question:** Please clarify why different degrees of response were not modelled – for example responses where BVAS/WG=0 but prednisone had not reduced to zero? The ERG's clinical advisors suggest that patients who achieve this type of "partial" response may be clinically significantly different from patients who do not achieve a BVAS/WG score of 0. For instance, such patients may be in remission, but may remain on steroids to control a certain aspect of their disease. However, in the economic model these patients are classified as not being in remission.

We considered the primary outcome of the RAVE study to be the most relevant definition of remission. We chose not to explore different degrees of response and the effect on a patient's quality of life. We recognise the definition in the RAVE study may be more restrictive than the definition for remission within clinical practice.

In order to expand our analysis to assess the different definitions of response we will need to review and map the utilities used for patients in the remission and non-remission health state. Whilst we are happy to undertake this, we cannot complete this substantial work ahead of the clarification question deadline. We will, however, endeavour to complete it as soon as possible if the ERG considers this relevant to the decision problem.

30) **Priority request:** Please comment on the face validity of the results of the economic evaluation: For the new patient subgroup (approximately half of all patients) the ICER is approximately £60,000 per QALY gained, for previously treated patients (the remainder of patients) the ICER is approximately £47,000 per QALY gained, yet for all patients combined the ICER is approximately £11,000 per QALY gained. Why is the ICER for all patients not between the ICERs for the two individual subgroups?

As noted in question 20, relapse rates were not calculated on patient level data; rather they were based on summary data from the clinical study report. As the subgroups had relatively low patient numbers, all estimates are subject to uncertainty and should be interpreted with caution.

31) **Priority question:** Please clarify why different relapse rates were not used in the economic model after first and second relapses (as differential rates are used in the new and previously treated patient subgroup analyses).

In our subgroup analyses of new and previously treated patients, we did not apply differential rates of relapse after the first and second treatment course. As noted in question 20, we believe that the relapse rates in the pre-specified subgroups should be interpreted with caution due to the low patient numbers. For this reason, we do not consider them reflective of a patients probability of relapse after one or two courses of treatment. As the RAVE studied evaluated induction therapy, we do not have the evidence to inform a patients relapse rate following a second course of treatment. For this reason we consider it appropriate to apply a constant rate of relapse for both treatment arms in the analysis.

32) **Priority request:** Please clarify why the utility score for the "uncontrolled" health state was not varied in probabilistic sensitivity analysis (its value is hard-coded in cell D102 of worksheet "PSAInputs" in the model).

This is due to a programming error. Please see Figure 1 and Figure 2 displaying the cost-effectiveness plane and CEAC results, respectively, based on the updated PSA where the utility score for the uncontrolled disease health state was varied. The results show the model remains robust to parameter uncertainty.

Figure 1:Cost-effectiveness plane (updated PSA - varying utility of uncontrolled disease)

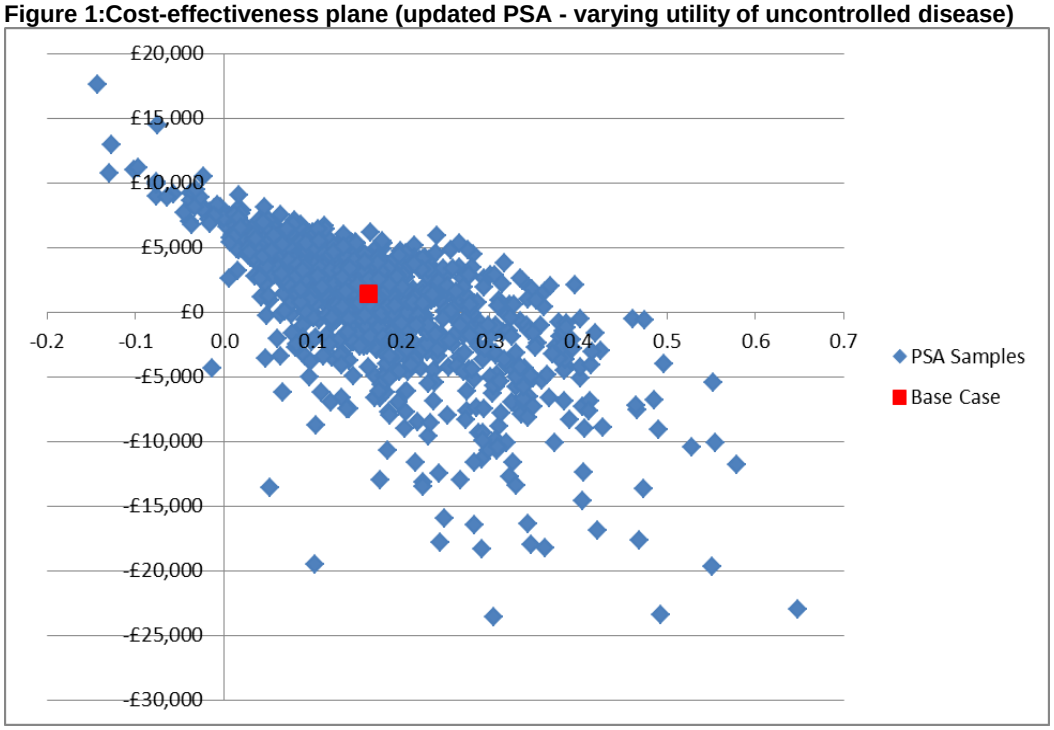
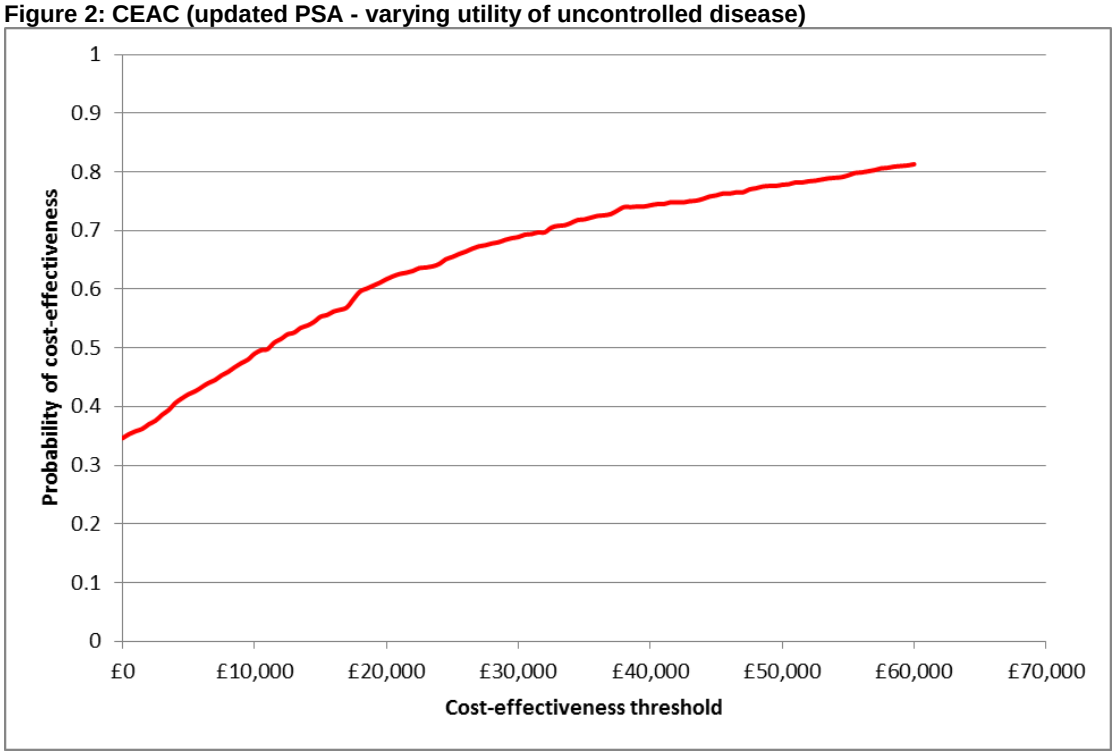


Figure 2: CEAC (updated PSA - varying utility of uncontrolled disease)



33) **Priority request:** Please check the numbers in Table 51, and the corresponding numbers in the model: The BNF March 2013 lists the price of 56 *50*mg tablets of azathioprine to be £5.04, not 56 *25*mg tablets. Also, the cost/mg for RTX and AZA appear to be incorrect. Also, clarify why methotrexate and mycophenolate mofetil are included in this table but not in the model.

The AZA price for the 50mg tablets has been corrected in the analysis. By correcting this error the ICER is increased to £11,583. The costs per mg of RTX and AZA are tabled below. The minor rounding errors reported in the submission were not present in the model and therefore had no effect on the ICER. As noted by the ERG, the costs of MTX and MMF are not used in the model.

Cost per mg (£)	Original Submission	Corrected version
RTX	1.73	1.75
AZA (25mg)	0.004	0.01
AZA (50mg)	0.02	0.002

34) **Priority request:** Please clarify why the cost of a pack of 30 1mg prednisone tablets is used in the model and in Tables 51 and 52, rather than the cost of 2mg or 5mg 30 tablet or 100 tablet packs (which have much reduced costs per mg). This is particularly relevant considering the initial dose of prednisone given in RAVE was 1mg/kg/day and the average dose per cycle is stated to be 3506mg.

We note that the alternative preparations could be used. An updated cost applying the average cost of all the preparations has been calculated. This amendment reduces the ICER. The updated per mg prices of prednisone are shown in the table below.

Prednisone	**Number of tablet**	**Price**	**Cost per mg (£)**
1mg	30 tab	£26.70	0.89
2mg	30 tab	£26.70	0.45
	100 tab	£89.00	0.45
5mg	30 tab	£26.70	0.18
	100 tab	£89.00	0.18
Average			**£0.43**

35) **Priority request**: Please justify why NHS reference cost SD04A was used to reflect best supportive care in the "uncontrolled disease" health state. Are any other cost sources available? Please confirm that where the frequency "*1.5 times weekly*" has been stated for this cost and those presented in Table 55, you actually mean "1 appointment every 1.5 weeks".

Based on clinical opinion, patients will eventually exhaust all treatment options. Since these patients remain with active disease, the model anticipates they will continue to receive on-going care, until death. Based on the definition provided by the department of health for the SD HRG (Subchapter SD, Specialist Palliative Care (SPC) relates to care in which the clinical intent or treatment goal is primarily quality of life for a patient with an active, progressive disease with little or no prospect of cure) and on the basis that this service included clinical consultancy, the model uses the NHS reference cost SD04A.

Table 2 shows results of one way sensitivity analysis where the cost of uncontrolled disease was varied. Scenario A assumes patients would receive a consultant cost (other body organ involvement) and scenario B assumes patients would accrue the same cost as patients in non-remission. The sensitivity analysis demonstrates RTX remains cost-effective.

The frequency employed in the model is once every 1.5 weeks.

Table 2 OWSA (Cost of best supportive care)

		CYC arm		RTX arm				
		Total costs	Total QALYs	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER
Base Case	Assumes patients in uncontrolled disease receive best supportive care cost (£254)	£95,819.17	8.0296	£97,210.20	8.1924	£1,391.03	0.1628	£8,543.69
Scenario A	Assumes patients in uncontrolled disease receive consultant cost (other body organ involvement) (£125.68)	£58,673.29	8.0296	£63,893.61	8.1924	£5,220.32	0.1628	£32,063.14
Scenario B	Assumes patients in uncontrolled disease receive non-remission health state cost (£6312)	£127,387.75	8.0296	£125,524.44	8.1924	-£1,863.31	0.1628	RTX dominates

36) **Priority request:** Please provide further justification for the existence of an “uncontrolled disease” health state, in which patients do not receive any specific treatment for relapses, and which patients currently transit to after two courses of CYC. In Section 7.3.1 it is stated that details on this health state were informed by clinical expert opinion. Does any supporting evidence exist?

We do not have any supporting evidence for this health state. When constructing the model we considered it unreasonable that patients would go on to receive continued therapy considering the toxicity associated long term CYC.

Clinical opinion was sought whether it was reasonable to assume that within a patient’s journey with this disease that they will exhaust all treatment options. The clinician was supportive with the concept that not all patients with obtain remission and that most will eventually relapse on current standard of care. They were also supportive of the concept that it was unreasonable to assume unlimited challenging of CYC due to the cumulative toxicities associated with its continued use. The clinical expert we contacted noted, that in his practice he would prescribe maintenance therapy RTX, however as discussed this falls outside the licence and scope of this appraisal.

37) **Priority request:** Please clarify the justification for assuming that RTX and IV CYC monitoring occurs during the administration appointment – given that clinicians may wish to see the results of monitoring tests before proceeding with the administration. Clinical advice received by the ERG suggests that monitoring of patients treated with rituximab may be required in the long-term, after treatment discontinuation, due to limited evidence on long-term side effects. Please clarify why this has not been included in the economic model.

The cost of IV infusion is per cycle and is a composite of administration and monitoring costs. Whether monitoring occurs at the time of administration or later is irrelevant since both are assumed to occur within the cycle, at the same frequency.

38) **Priority request:** Table 52 suggests that the same average dose of methylprednisolone and prednisolone is assumed for RTX and CYC, taken from the RAVE trial. Please clarify whether the average doses of these drugs received in the two treatment groups were the same in the trial.

The average doses received by each treatment group were not substantially different, hence a weighted average dose was assumed for the model. Table

3 presents results where the actual doses are used in the model, showing RTX is more cost-effective.

Table 3 Methylprednisolone and Prednisolone

	CYC arm		RTX arm				
	Total costs	Total QALYs	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER
Base case: Weighted average dose	£94,025	7.7148	£96,656	7.9500	£2,631	0.2352	£11,189
Actual doses reported in CSR	£94,335	7.7148	£96,579	7.9500	£2,243	0.2352	£9,538

39) **Priority request:** Please clarify how many patients had died in each arm of the RAVE trial at the longest data cut.

At the 18 months data cut there were 4 deaths reported, 2 each treatment arm.

40) **Priority request:** Please clarify why the base case analysis (and seemingly all subgroup analyses) presents cost-effectiveness results based on point estimates of parameters rather than expectations of the mean (from the probabilistic model).

We have reserved probabilistic mean input parameters for the PSA section of our submission, and then only applied to the base case. All of our point estimates come from the summary statistics in the clinical study report rather than patient level data. Bootstrapping new mean values from assumed distributions about each parameter is, in our view, most useful only if one simultaneously considers the uncertainty generated. That said, should the ERG wish to see any (or all) of our subgroup analyses repeated with probabilistic mean values, we would be happy to provide this.

41) **Priority request:** Please justify why the standard error is assumed to be 30% of the mean in rows 11-16 of the “PSAInputs” worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts upon the formulas used to estimate the alpha and beta values for the beta distributions. Finally please explain why standard errors were not estimated based upon the exponential model fits for relapse rates. The ERG suggests that these beta distributions have a very important impact upon the probabilistic analysis.

We have revised the method used to calculate the alpha and beta values in the economic model. The original model used the methods outlined by Briggs et al 2006, using mean and standard error/variance (p88-89), for which the standard error was assumed to equal 30% of the mean. In the revised model we have alternatively calculated the alpha and beta values by applying the mean probability of relapse (as determined from the exponential model) to the sample size of each treatment group and subgroup; overall this has a modest effect on the standard errors estimated.

42) **Priority request:** Please clarify and justify why a Markov model (with underlying assumptions of exponential sojourn time) was used, particularly given the seemingly poor fit of the exponential models used to estimate relapse rates.

As previously expressed, in the face of relatively scarce clinical data and considerable uncertainty, we opted for a simple model structure and assumption set which could be extensively diagnosed with sensitivity analysis, rather than a more elaborate model structure whose complexity might in fact hinder a clear understanding of the main limitations and dependencies.

We recognise that there may have been similar merit in building a model whose relapse profiles more exactly fit the extrapolated curve, but considering the uncertainty of our assumptions around relapse over time in the first place (including how this parameter should be extrapolated) we concluded that the extra work was not justified.

Section 2: Lower Priority Questions and Requests

Literature searching

1) Section 10.2 Appendix. The search appears inconsistent and thus inadequate. Some databases are limited to searching for the population only, e.g. Cochrane, whereas others are interrogated for population and intervention. Please clarify why this is the case.

Roche recognise that only the population was searched in the Cochrane Library. On reflection, Roche has taken the decision to run the search in the Cochrane Library again to include search terms for population and intervention. The search strategy and results and attached in the appendix of our response.

2) Please state the total number of records identified through database searching prior to the removal of duplicate titles in the PRISMA flow diagram presented in Section 2.2.2. Also please explain which sources were used in addition to database searching as shown by "*additional records identified through other sources*".

The total number of hits identified in the search via ProQuest completed on 11/03/2013 was 1149 [search strategy was exported from ProQuest on 11/03/2013 and included in the original submission]. Additionally, 10 hits were identified from other sources which were articles cited in reference lists not retrieved in other searches. 136 hits were identified from the Cochrane database searched on 08/03/2013. A total of 134 hits were retrieved from PubMed on 28/01/2013.

Therefore, the total number of hits retrieved was 1429. These numbers have been included in the updated PRISMA diagram attached.

3) The subject heading ("ANCA associated vasculitis") usage described in Tables 73 and 74 of Appendix 1 is somewhat restrictive. Please state the entry date used for this heading in the searches. This is important because the thesauri year of entry for the subject heading of "ANCA vasculitis" is 2010 (Medline, Ovid) and 2005 (Embase, Ovid), respectively (previously records were indexed under "Vasculitis").

As highlighted, the date of entry for "ANCA associated vasculitis" was added as a MeSH term and EmTree term in 2010 and 2005 respectively.

Roche accepts this point raised by the ERG as a limitation of the search strategy presented in Table 73 and 74 of the submission and has taken this opportunity to re-run the literature search. The thesauri term for "Vasculitis"

and free text term “small near/3 vessel near/2 vascul*” has been included in the search strategy. Please find details of the literature search attached.

In brief:

Summary of results of the literature search
A total of 1404 records were retrieved from Medline, Medline-In Process, Embase and Embase Alerts and 12 records were retrieved from the Cochrane Central Register of Controlled Trials. Therefore, a total of 1416 records were retrieved for the literature search. Of these records, 340 were identified as duplicates. A total of 1076 unique records were available for screening and subsequent exclusion with reasons. At screening, 973 records were excluded. This means that 103 records were eligible for full text assessment. A total of 68 records were subsequently excluded with reasons. This means that 35 records were included in the systematic literature review. A number of these records related to the same study and this is indicated in the attached table.

This re-run of the literature search did not identify any new publications for consideration in the STA submission.

4) The intervention term usage described in Table 74 of Appendix 1 is not comprehensive – alternative terms for rituximab were lacking. Please update the search using the full range of terms that may be used to describe rituximab and clarify whether any additional evidence is found.

Roche recognises that the search terms used for the search strategy presented in Tables 73, Table 74 and Table 75 of the submission are restrictive and has taken this opportunity to re-run the literature search. This search addresses the points made in section 2, questions 1, 3 and 4.

<u>Section A – Description of the technology, context, equality, innovation and the decision problem</u>

5) In Section 2.5 it is stated that “*Patients may continue maintenance therapy/immunosuppression for up to 5 years*”. Clinical advice received by the ERG suggests that in fact maintenance therapy may last much longer than 5 years. Please clarify this, and also comment upon how this is captured in your economic analysis.

As per the protocol in RAVE, patients in the economic model who have achieved remission following CYC go on to receive maintenance AZA therapy until relapse. Patients who achieve remission following successful induction therapy with RTX do not receive maintenance therapy in line with the RAVE protocol. We note that the EULAR guidelines {Mukhtyar et al 2009] state that ‘*remission maintenance therapy should be continued for at least 18 months*

(especially in WG). Recently published guidelines by the British Society for Rheumatology recommend maintenance therapy be continued for at least 24 months.

Section B – Clinical Effectiveness

6) With regard to the exclusion criteria presented in Table 6, please provide a justification for each to ensure that the rationale for exclusion is transparent.

We have attached the justification for the exclusion criteria in the clinical search strategy in Table 6 in the appendix.

7) Figure 1 appears to only present the results of the Embase/Medline search from Appendix 10.2. Please present results that include the Cochrane and PubMed searches (270 more citations), or clarify why these results do not seem to be included in Figure 1.

We have completed the PRISMA flow diagram an attached the diagram with our response.

8) Figure 1 states that 45 full-text articles were excluded. Please provide a full list of these studies with reasons to explain their exclusion.

The list of 45 excluded studies is attached.

9) Please comment upon the ability to make statements upon the effectiveness of rituximab in patients with life-threatening disease (for example, those with pulmonary haemorrhage or active central nervous system vasculitis), given available evidence.

GPA and MPA are known to be progressive and potentially fatal diseases when untreated, and are considered to be life-threatening diseases even though patients may not be immediately admitted to the ICU. The mortality in RAVE and RITUXVAS ranged from 2-18% over 2 years, and RITUXVAS enrolled older patients with more renal involvement – 2 factors associated with mortality independent of treatment.

These 2 studies suggest that rituximab is effective in multiple clinical life threatening scenarios, and also in patients refractory to CYC.

Patients with the most severe forms of pulmonary haemorrhage were excluded from both RAVE and RITUXVAS because mortality is high and physicians are generally reluctant to recruit critically ill patients to this type of trial. However, time to remission for patients with less severe lung haemorrhage was a secondary end-point in RAVE and there was no

difference between CYC and RTX groups. Expert opinion believes that there would be no reason to think responses in severe pulmonary haemorrhage would be any different.

Expert practice, and their advice to others, is to use rituximab for the most severe forms of pulmonary haemorrhage because the major cause of death is infection in the second or third intensive care week and they regard the infection risks of RTX and steroids as being easier to manage than those with CYC and steroids.

Central nervous system vasculitis; vasculitis of the brain is rare in ANCA vasculitis and rarely life threatening. It is very rare in microscopic polyangiitis. In GPA (Wegener's) you do sometimes see a pachymeningitis, pituitary or hypothalamic lesions, cranial neuropathies and involvement of the optic tracts within the brain, and rarely direct extension of granulomatous disease from the sinuses into the cerebral hemispheres. The pathology is granulomatous and the response to RTX in line with the response of granulomatous disease in the ENT region or the lung.

In RITUXVAS, patients with the most severe forms of renal disease were included, and these responded the same to the RTX regimen as to the CYC regimen. The pathology of pulmonary haemorrhage in AAV is an alveolar capillaritis identical to the pathology of nephritis in AAV.

The clinical expert we contacted considered he would use this evidence plus the extrapolation from the RAVE data to say that life threatening lung haemorrhage is likely to respond to RTX in the same way.

10) In Table 9, it is stated that patients intolerant to CYC were excluded from the RAVE trial. The ERG suggest that this makes any analysis of CYC intolerant patients based upon the RAVE trial inappropriate. Please comment upon this point – is any data available on patients intolerant to CYC who have been treated with RTX?

There are no randomised studies evaluating the effectiveness of RTX in CYC intolerant/contraindicated patients. Expert opinion noted the evidence in Jones et al (Arthritis &Rheum 2009) and Smith et al (Arthritis &Rheum 2012) demonstrates that the response rates for RTX are good in this population. However, these studies do not distinguish between CYC intolerant/refractory/high exposure.

Expert opinion noted that intolerance to CYC is very rarely related to hypersensitivity, but more a general dislike to using the treatment. One of the most identifiable patient groups in this ‘CYC intolerant’ group, as noted at the

scoping workshop are those patients who are looking at preserving their fertility. This patient population could well receive CYC, however the consequences of this decision are difficult to capture within the QALY as noted in section 4.1.2 of the submission.

We believe that there remains a high unmet need for an alternative induction agent where CYC is not considered appropriate. The evidence for this group is extremely limited, but clinical opinion considers there to be no a priori reasons for thinking the RTX response will be any different between CYC tolerant and intolerant patients.

11) Please clarify whether data are available on how many courses of CYC treatment (or what lifetime dose of CYC treatment had so far been received) had been received by patients who had previously used CYC that were recruited into the RAVE trial. Related to this, how many relapses had these patients had prior to trial entry? Please comment upon whether these patients fit within the proposed rituximab licence.

Data are available on prior CYC exposure from the database, but historical data was not deemed particularly reliable and only limited analyses occurred. The data that were collected were whether the patients entering RAVE were newly diagnosed or experiencing a severe relapse, and whether they'd previously received CYC for GPA or MPA disease. An analysis of CYC exposure was done for the patients experiencing malignancy, and this was reported in the Supplement to the NEJM 2010 RAVE publication (this was attached in the original submission). Number of CYC courses, lifetime exposure, and number of prior relapses were variably collected in the AAV specific medical history, but have not been systematically analysed.

The assumption surrounding the number of CYC courses a patient would receive was supported by expert clinical opinion.

12) Please clarify the justification for the use of the BVAS/WG outcome measure, considering that it has only been validated in WG patients. Please comment upon the implications of using this measure in MPA patients. Please clarify why the BVAS/WG measure was used instead of the validated BVAS measure and provide citations on the validation of the BVAS scale.

There is significant overlap in the clinical presentations of MPA and GPA such that experts in the field of vasculitis research have combined these populations in multiple trials over the past decade given the rarity of these diseases. The BVAS and the BVAS/WG have been applied to both populations, and Roche agree with the ERG that formal validation of

BVAS/WG has only occurred in WG patients. However, the major and minor items included in the instruments have captured clinical events reliably in both populations, and the instruments have also included an “Other” field to allow inclusion of events that could theoretically occur in MPA patients alone.

A recent review by Lionaki evaluated the classification schemes used to identify patients with these diseases (Arthritis Rheum. 2012 Oct;64(10):3452-62. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Lionaki et al. Figure 2 in this reference clarifies that the proportions of patients with symptoms of MPO-ANCA disease or PR3-ANCA disease varies, yet neither disease has features completely exclusive of the other.

The BVAS (version 3) went through a validation exercise and was published in 2009 (Ann Rheum Dis. 2009 Dec;68(12):1827-32. Modification and validation of the Birmingham Vasculitis Activity Score (version 3).Mukhtyar et al). This exercise included 155 GPA patients, and only 15 MPA patients, yet was considered acceptable for both populations.

The BVAS/WG (A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS).Stone et al. Arthritis Rheum. 2001 Apr;44(4):912-20.) is a modification of the BVAS and was generated for the WGET trial to reduce redundancy of specific items, enhance the ability to capture specific symptoms, generate greater discrimination of newly occurring items vs persistent features and streamline the instrument for greater reliability when applied to large multicentre studies. BVAS has been further modified to version 3, demonstrating an interest in revising the original instrument as greater data was collected on instrument performance from clinical trials. The BVAS/WG was used in the WGET trial -the first trial of a biologic agent in GPA/MPA,and this experience carried it forward into the RAVE trial design.

BVAS/WG has been accepted by the vasculitis community as the primary instrument in the PEXIVAS trial. This is the largest international trial of GPA/MPA (n=500) enrolling across EUVAS and VCRC sites in addition to sites in Australia and Asia and is expected to enroll a significant number of MPA patients.

13) In Section 6.3.6 it is stated that a “*worst case*” analysis was undertaken whereby data for patients who switched treatments were imputed as treatment failures. Clarify why this is a “*worst case*” analysis,

considering that it was previously stated that early treatment failure triggered treatment switch.

This was a sensitivity analysis wherein the primary endpoint was also determined using worst-case imputation for ITT patients who discontinued permanently from study treatment or withdrew from study before Month 6, without having already been classified as treatment failures. This differs from a 'last observation carried forward' imputation wherein achievement of complete remission would have been recorded if the patient achieved the criteria yet dropped out before the 6 month timepoint.

Assigning treatment failure to dropouts in this manner provides a 'worst case' view of their clinical outcome. This doesn't significantly differ from early treatment failures that crossed over, because these patients would have also been assigned to treatment failure. 'Worst case' implies that all possible scenarios (even treatment success, followed by drop-out) are not categorized as benefit.

14) Please provide more information on the "*anomalies*" identified in the clinical data referred to in Section 6.3.6.

The data review committee identified a number of anomalies in the clinical data after the original unblinding and reporting of the study results. At the recommendation of the data review committee, changes were made to the analysis datasets to correct the anomalies of most concern.

Roche do not have the descriptions of the individual anomalies, but have provided a summary of the minor numerical changes to some long-term efficacy endpoints at the 12- and 18-month time points (summarized in the appendix). The differences did not alter the data interpretation or overall conclusions. The 6-month results were not affected.

15) With respect to Section 6.4, the non-inferiority extension to the CONSORT statement should have been applied and used as a critical appraisal tool (Piaggio, *JAMA*, 2006). Please clarify why this checklist was not used.

Roche apologise to the ERG for not using the non-inferiority checklist to the CONSORT statement. This was an oversight by Roche; the table showing the additional items on the checklist is attached.

16) Tables 15, 16 and 21 refer to the "*ITT Population*", but exclude patients with "*missing*" data. In addition, patients who failed treatment prior to 6 months were excluded from the "*primary efficacy analysis*". Please comment on the susceptibility of these analyses to selection bias.

The RAVE study “primary efficacy analysis” excluded patients who were missing data for the assessment of complete remission at 6 months (as pre-specified in the statistical analysis plan). This affected only 4 patients and the results are shown as the first set of results in Table 15 as well as in Table 16. In a pre-specified “sensitivity” analysis, worst case imputation (WCI) was applied to missing results; in other words, these 4 patients were imputed to have failed to achieve complete remission at 6 months. The latter approach, shown as the second set of results in Table 15, is perhaps more traditional for a primary endpoint analysis (ITT) and these are the results shown in the EU Summary of Product Characteristics. These two approaches have made very little difference to the point estimate for the RTX versus CYC treatment difference (9.5% excluding missing data, 10.6% using WCI) or to the lower 95.1% confidence limit (-4.3% excluding missing data, -3.2% using WCI). Patients who failed treatment prior to 6 months were not excluded from the primary efficacy analysis, which included these patients using an “as defined” approach; they were considered as failures to achieve complete remission at 6 months regardless of treatments received and BVAS/WG score achieved by 6 months. Neither were they excluded from a sensitivity analysis that used an “as treated” approach, whereby patients who met the “early treatment failure” definition of the protocol but remained in their original treatment arm could still achieve the primary endpoint at month 6 if BVAS/WG score = 0 and glucocorticoid tapered to 0. The “as defined” (primary analysis) and “as treated” approaches were pre-specified in the statistical analysis plan and reported in the RAVE Clinical Study Report and the EU Summary of Clinical Efficacy.

17) Please clarify the flare rates presented in Table 21 (that are also presented in Table 15). A footnote to Table 21 states that flare assessments for patients during crossover were excluded from the analysis. In Section 6.3.2, it is stated that patients who experienced severe disease flares or treatment failure between Visit V5 and Visit V8 (month 6) were crossed over to the opposite treatment arm. Please confirm the timing of Visit V5, and clarify whether disease flares that triggered treatment switch are included in the figures presented in Tables 21 and 15.

The timing of V5 is Month 1 (day 29) .The investigators wanted to discriminate between persistence of a high degree of clinical activity present at randomization from a future flare, which implies that disease activity improved before it worsened (flare) Disease flares that triggered treatment switch are included in Tables 21 and 15.

Flare assessments for participants during receipt of crossover treatment, open-label Rituximab or following a switch to best medical judgment are excluded from these analyses.

18) The majority of the additional analyses described in Section 6.5.1 (for example, Tables 25-30, Figs.7 and 8), were neither clearly pre-specified nor address the decision problem (decision problem subgroups were only *de novo* patients; CYC-relapse patients; and CYC contraindicated patients). Please clarify and justify the inclusion of these analyses.

As discussed previously, these additional analyses were pre-specified and listed in the Statistical Analysis Plan:

- Table 25: Complete remission at 6 months for patients either with or without one major major renal item on BVAS/WG at baseline (ITT population)
- Table 26: Complete remission at 6 months for patients with creatinine clearance values <60 ml/min or ≥60 ml/min at baseline (ITT population)
- Table 27: Complete remission at 6 months for patients with creatinine ≤ or > 1.2 mg/dl (ITT population)
- Table 28: complete remission at 6 months for patients either with or without alveolar haemorrhage at baseline (ITT population)
- Table 29:Complete remission at 6 months for patients with either MPO or PR3 antibodies at baseline (ITT Population)
- Table 30: Change in ANCA status by treatment arm (ITT population)

Roche agree with the ERG that the data was not directly part of the decision problem, but Roche believe that the data serve to address issues of importance to subgroups of patients with AAV and may help clarify further questions which could be raised at the ACD meeting.

Roche agree with the ERG that, with hindsight, figures 7 and 8 from the RITUXIVAS Study should not have been included in the STA submission.

- Figure 7: RITUXVAS BVAS score distribution
- Figure 8: RITUXVAS weight-adjusted prednisolone doses

19) In Table 32, please clarify what Group C refers to in the description of the Smith *et al* 2012 study.

The Smith et al., 2012 publication described a single centre retrospective, standardised data collection from sequential patients receiving rituximab for refractory or relapsing AAV. Group A (n=28) received rituximab induction (375mg/m^{2}x4 or 2x1g), and further rituximab at the time of subsequent relapse. Group B (n=45) received routine rituximab re-treatment for two years; 2x1g induction, then 1g every 6 months (6g total). Group C (n=19) comprised

Group A patients who subsequently relapsed and commenced routine re-treatment for two years.

Section C – Economic evaluation

20) Please clarify whether all relevant co-medication and pre-treatment costs are included in the model – for example, premedication with analgesic/anti-pyretic/anti-sickness drugs, anti-histaminic drugs, and PCP prophylaxis.

The economic analysis has captured the co-medication and pre-treatment costs used within the RAVE study (methyprednisone, prednisone, and trimethoprim).

21) Please clarify whether all relevant adverse events have been included in the economic model, and explain why a number of serious AEs mentioned in Section 2.3 do not appear to be in the economic model.

All relevant AE were taken from the RAVE study. Section 2.3 does accurately describe a range of longer term adverse events that were not captured within our analysis. Most of these AE relate to the cumulative toxicity associated with CYC and prolonged use of glucocorticoids.

Identifying which patients may be subject to the longer term AE related to continued use of CYC or glucocorticoids is extremely difficult and therefore has not been incorporated into the analysis

22) Please provide justification for choosing a lifetime horizon for the analysis – please describe how and why the treatment sequence impacts upon survival, with supporting evidence.

A lifetime horizon was considered appropriate as AAV and the therapies used to treat it, are likely to lead to long-term differences in survival and quality of life.

23) Please provide justification for the use of the Lane *et al* (2005) study to model mortality risks over time. The Lane *et al* (2005) study identified 99 patients with AAV between 1988 and 2000, and therefore the data are dated.

- Please comment on the impact that the age of this cohort data may have on its validity to be used to model present-day and future survival of patients with AAV, taking into account issues such as

treatment and dosing regimens and any trends in survival over time.

- In addition, only 31 deaths were observed and patients were not classified as regards whether they were in remission or not – please comment upon the uncertainty associated with these data and their importance in the economic model.

The survival data from Lane et al represents a reasonable estimate of survival for patients with AAV. While the ERG correctly notes that the cohort of patients within the study was between 1988 and 2000, the standard of care has changed very little over that time. We note that CYC has been the standard of care for 40 years.

We note there are a number of limitations associated with this data that are outlined within our submission. We acknowledge that we were unable to accurately match outcomes within the Lane study to the health states within our economic model and therefore fully accept the limitations.

In the sensitivity analysis the mortality assumption was tested (Table 67).

24) Please clarify whether any other data exist to support the mortality assumptions used in the economic model. Please justify the assumption that patients in complete remission have a lower risk of mortality.

As noted in question 24, we recognise the limitations in the evidence supporting the mortality assumptions. This assumption has been tested within the sensitivity analysis reported in Table 67 of the submission. The model was not sensitive to changes in the mortality rate assumptions.

Expert clinical opinion that supported the notion that those patients in clinical remission would have a better prognosis than those in poor disease control.

25) Please clarify whether the use of the arbitrary ±10% applied to the estimated SMR taken from the Lane *et al* (2005) study for the uncontrolled and remission health states will lead to the average SMR implied by the model being different from the 4.8 estimated by Lane *et al* (2005) (due to the different proportions of time spent in these states in the model).

According to Lane et al. (2005) the SMR for vasculitis patients comparing to the general population is 4.8 for a 10-year period between January 1989 and December 1998. In our model the estimated 10-year SMR is 4.5. The 0.3

difference in the model is primarily driven by the fact that, for simplification the SMR estimates are multiplied at each cycle. This leads to a small underestimate of patients at risk at each cycle and therefore a lower average SMR at the end of 10 years. The difference in SMR between the two arms, driven by the health state transitions and the differential ±10% assumption, is 0.068.

26) Please clarify why the Barton *et al* (2004) reference has been used for the cost of RTX administration – a cost estimated for the administration of infliximab with a price year of 2000. Are more relevant and recent estimates available?

The reference cost from Barton et al has been commonly used within recent rheumatoid arthritis appraisals for the cost of infusing non-oncology treatments. While it was sourced in 2000, the figure has been adjusted for inflation.

27) Please clarify how the data that suggest that 72% of CYC given is by IV were obtained. How many clinicians/centres were surveyed?

Roche employed a third party agency to undertake market research in 2012. The agency contacted 50 Nephrologists and 50 Rheumatologists represented across the UK (please see table below for geographical representation). All respondents had to treat AAV, with a mix of respondents having used RTX to treat AAV. All clinicians were either Consultants or Specialist Registrars.

Geographic Centre	**Number of Respondents**
North England	31
Midlands	25
South England	25
Devolved Nations	19

28) Please clarify what the comparator treatment was in the subgroup analysis for patients intolerant to CYC. In Tables 4 and 70 the comparator is labelled as “CYC”, yet this is for patients who are intolerant to CYC.

- Do patients in the “CYC” arm transit immediately to the “uncontrolled disease” health state?
- Please clarify why alternative comparator treatments were not considered for this subgroup.

The labelling should refer to best supportive care and not CYC. The subgroup was identified at the NICE scoping workshop, where both clinical experts and patients group representatives discussed the small patient group that could

not tolerate CYC for a variety of reasons. Clinical opinion was this group was extremely small, likely to be less than 10% of the licensed population (refer to question 10 for more details).

The model has modelled the effect of RTX compared to best supportive care (patients transition to uncontrolled disease immediately).

29) Please justify why only the events included in Tables 40 and 41 are relevant for the economic model. Please justify why adverse event rates at 6 months were used instead of adverse event rates at 18 months. Since AZA treatment is given during the remission phase please justify why the data presented in Table 42 refer to the 6 month time-point.

The AEs listed in Table 40 and 41 were based on a case study report from the RAVE study reported within the first 6 months. We note that overall the safety profiles were considered comparable between RTX and CYC in RAVE. Roche are willing to update the safety data in the model using the latest data cut from the RAVE study within the economic model if the ERG request.

Table 42 has been incorrectly labelled. A review of the RAVE data was undertaken and identified the AE rates included in the model for patients on AZA therapy (post 6 months).

30) Please clarify and justify the duration assumed for the AEs included in the model.

Adverse events were assumed to occur for the duration of a cycle, with patients facing probabilities of treatment-related AEs only whilst on treatment. If they switched treatments, they would face risks of adverse events related to the new treatment.

31) Please comment on the face validity of allocating lower adverse event costs to rituximab in the economic model, given that it is noted in Section 6.8.2 that hospitalisations associated with study drug were more frequent in the rituximab group. Is this adequately reflected in the economic model?

As noted in section 6.8.2 of the submission, hospitalizations were a subset of serious adverse events, rates of serious adverse events and serious infections were balanced across treatment groups. It is therefore not unreasonable to assume that CYC AE costs might be higher than RTX. We note that the overall difference in the model is estimated at £26.36.

32) The ERG notes that the economic model includes inputs for malignancies, but these are not actually part of the functional economic model. Please clarify why this is the case.

The model developed was originally designed to include any malignancies identified within the RAVE study. However after further review of the evidence we noted that only two incidents were reported and neither could reliably be related to RTX. Therefore the malignancies were not included within our economic model.

33) Please clarify why 2009-10 reference costs were used, rather than more recent data, e.g. 2011-2012 costs.

The model was originally developed in 2011 and used 09-10 reference costs. In not updating the reference costs to the most recent data we do not believe that the result will change significantly.

34) Please provide justification for the statement made in the second paragraph of Section 7.2.5 that "*These limitations we believe may lead to an underestimation of the true benefit of successful induction therapy*".

We have hypothesised in the above statement that induction treatment with either CYC or RTX may lead to greater benefit if the true morbidity and mortality associated with avoidance of irreversible damage to particular organs could be accurately modelled. We note earlier in the paragraph in section 7.2.5 as to the reasons why this was not possible, identifying a number of evidence gaps and methodological challenges.

35) Please clarify whether the numbers presented in Table 37 are correct – for rituximab they do not appear to match the figures in the economic model.

The corrected figures in the submission are outlined below in bold.

Transition Probabilities	**Value**	**Source**
Newly diagnosed Subgroup		
Complete remission (CYC)	0.6458	Stone et al, 2010
Complete remission (RTX)	**0.6042**	Stone et al, 2010
Relapsing Patients Subgroup		
Complete remission (CYC)	0.4200	Stone et al, 2010
Complete remission (RTX)	**0.6667**	Stone et al, 2010

36) Please clarify whether the * is in the wrong place in Table 40.

The asterisk should be positioned on the final row related to DVT.

37) Please clarify why a standard error is given for Imaging in Table 43, but not in the economic model.

This is an error. No standard error value was used within the economic model for the imaging cost. We were not able to source a value of uncertainty for this variable.

38) In Section 7.3.8, it is stated that an average body surface area of 1.79m^2 was assumed based upon an estimate for UK cancer patients, rather than the body surface area observed in the RAVE trial. Please justify why UK cancer patients are thought to provide a good proxy for AAV patients. Are any other sources of data available?

In addition to one of the known symptoms of AAV being weight loss it was considered that the average weight of patients in the RAVE study was considerably higher than what was deemed reflective of a normal UK patient (mean weight 87kg).

In Table 67 the BSA from the RAVE study was tested, this had the effect of increasing the ICER. However, as the cost of most treatments is weight based the increase in the ICER is relatively minor and not a key driver in the analysis.

39) In Section 7.4.5, it is stated that papers were included if utilities were derived directly or indirectly, yet in Figure 15 the inclusion criteria says only directly derived utilities. Please clarify which is correct?

Papers were included if utilities were derived directly or indirectly. We did not identify any studies which reported utilities related to AAV.

40) Please provide justification for the assumption that the difference in utility between the uncontrolled disease health state and the non-remission health state is the same as that between the complete remission health state and the non-remission health state. Why is there likely to be such a substantial difference between patients who are not in remission and patients who are “uncontrolled”?

The uncontrolled disease health state has been designed to reflect the cohort of patients who have failed or relapsed on all the available induction agents. We consider the utility estimate to be fair when considering the likely progression of the disease without the rescue of induction therapy.

For patients in remission who have a BVAS/WG=0 and are no longer on prednisone the quality of life is considerably better than those patients in the RAVE study who were not in remission. When considering those patients ‘not

in remission', this heterogeneous group contained patients in clinical remission but still on prednisone, and patients who may have some or very little organ involvement but otherwise feel fine. We would therefore expect that those patients at the other end of the spectrum in the non-remission health state with greater organ involvement to have a much poorer quality of life.

We would expect those patients with active disease without the further treatment to induce remission to have a much poorer quality of life than those patients in the non-remission health state. We have tested this assumption within our sensitivity analysis.

41) Please clarify why the numbers do not add up in paragraph 4 of Section 7.5.3 (i.e. 86 – 10 ≠ 78).

In total there were 8 duplicate records (5 from ProQuest and 3 from NHS EED) not 10 as reported within the PRISMA flow diagram.

42) Please clarify why the price for the 1g vial of methylprednisolone was used in the economic model, and in the numbers presented in Tables 51 and 52, rather than the price for the 2g vial (which has a lower cost per mg).

We agree that the 2g vial is slightly cheaper on a per mg basis than the 1mg vial. We have included the 2g in the updated version of the economic model.

Methylprednisolone	Cost	Cost per mg
1g	£17.30	0.01730
2g	£32.86	0.01643

43) Please check the numbers in Table 52: the average cost per cycle for AZA does not match what is in the model and needs to be corrected given the cost attributed to 25mg rather than 50mg azathioprine tablets in the model. Again clarify why methotrexate and mycophenolate mofetil are included in this table but not in the model. Also the * appears to be in the wrong place.

When applying the updated costs to the model, and the removing the monitoring costs that had been included incorrectly within Table 52 for AZA, the revised estimate is £44.17.

44) Please clarify your statement underneath Table 53 that: "*Since the cost of administering methylprednisone in the comparator arm is already included in the cost of infusing RTX, the model conservatively assumes*

zero cost for the administration of methylprednisone". Is this because methylprednisolone is given at the same time as RTX?

For IV administration of CYC and RTX, we assume that methylprednisone will be administered at the same time and therefore is already captured within the administration tariff in the model.

45) Please check the numbers in Table 55: some of these values are different from those in the economic model.

The imaging unit cost has been reported incorrectly in the submission and should be £29.08 per unit, with the cost per cycle in either health equal to £62.00.

46) Please clarify what the "*Probabilistic*" column of values in Table 60 represents.

This was an error on our part. We have accidentally provided a snapshot of the probabilistic sensitivity analysis input fields from our Excel model (column G in the PSAInputs sheet). These are live fields which update with new sampled values on every data refresh.

47) Please clarify the statement made in Section 7.9.5 – that an analysis of the relapsing disease subgroup was not undertaken. Analyses for patients who have previously relapsed prior to entry to RAVE *have* been presented in Table 69.

The ERG has correctly noted that we have presented subgroup analyses for both newly diagnosed and relapsing patients from the RAVE clinical trial.

48) Do the numbers reported in Section 8.2 refer to only severe ANCA-associated vasculitis patients, or all patients?

The numbers are reflective of those patients with severe ANCA-associated vasculitis.

49) Please justify why the standard error is assumed to be 20% of the mean in rows 19-22 and row 33 of the "PSAInputs" worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts upon the formulas used to estimate the alpha and beta values for the beta distributions.

No estimates of uncertainty were available for this parameter as it was a functional input used to ensure that the diminishing effect of repeated cycles of CYC was preserved in the PSA. The assumption that the standard error

was 20% of the mean was a relatively arbitrary one but it is not expected to have a significant impact on the results. The method of moments, as outlined by Briggs et al (2006), using mean and standard error / variance (p. 88-89), was employed to derive alpha and beta parameters.

50) Please clarify how the standard errors were calculated in rows 100-101 and 105-107 of the "PSAInputs" worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts upon the formulas used to estimate the alpha and beta values for the beta distributions.

A post-hoc analysis of data from RAVE was used to map SF-36 onto EQ-5D. Cells J100 and J101 present the values of the standard deviations of EQ-5D utility values for patients in these health states divided by the square root of their respective sample sizes.

No estimate of uncertainty was available from Borg et al (2008) for the utility value of anemia, therefore 30% of the mean was assumed relatively arbitrarily (J105). The range (0.35 to 1) presented in Wang et al (2008) for leukopenia was assumed to be the 95% CI and a standard error was estimated from it (J106). A standard error was now sourced from Mathias et al (1999) to inform uncertainty for the utility of DVT (J107). For all values, the method of moments, as outlined by Briggs et al (2006), using mean and standard error / variance (p. 88-89), was employed to derive alpha and beta parameters.

51) Please clarify why lognormal distributions rather than normal distributions were used for the reference cost data included in the model.

Both lognormal and gamma distributions can be highly skewed to reflect the skew often found in cost data. Both lognormal and gamma distributions were tested, and samples of the lognormal distribution appeared to represent the data better.

52) Please clarify why the probability of death associated with the uncontrolled disease health state becomes 1 in cell O208 instead of cell O210 in the "Mortality" worksheet of the economic model.

The probability becomes 1 in cell O208 because the probability of death in the general population (0.1676) multiplied by the upper CI of the SMR (6.6) is greater than 1.

53) Please clarify why rows 5 and 6 of the "PSAOutput" worksheet of the economic model only look at the first 100 samples, rather than all 1000.

This was a coding error, which has now been rectified.

54) Please describe how the analysis that included wastage was carried out, and provide costs for each drug. Did it assume that there was wastage associated with each administration, or with each course of treatment? The figure presented in cell H18 of the ”TreatmentCost” worksheet in the economic model appears to have been calculated on the basis that all four treatments with rituximab would be made up in one go, thus the potential wastage associated with each administration is not taken into account.

The wastage calculation was based on the treatment cycle and not on each administration. This has been updated and is presented in the updated analysis presented below.

Revised Economic Model

We have updated the economic model based on the ERG priority questions 32, 33, 34, and 41. In addition amendments were made based on the low priority questions 42, 50, 51, 52, and 53.

Base Case Results

Table 4: Base Case Results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) incremental (QALYs)
RTX	£97,819	11.82	8.19	£1,391	0.0422	0.1628	£8,543.69
CYC	£95,819	11.78	8.03				

Sensitivity Analysis

Table 5: Deterministic sensitivity analysis results

Scenario/parameter		Base Case	Tested values	ICER
CYC complete remission rate is equal to RTX		0.5306	0.6364	£24,656.29
Removal of degradation rate for CYC and RTX		CYC_2 - 0.4200 RTX – 0.4138	CYC_2 - 0.5306 RTX_2- 0.6364	£12,556.26
Standardised mortality ratio – set equal in all health states	NR CR UD	4.8 4.32 5.28	4.8	£7,835.98
Standardised mortality ratio – improve in CR and worsen in UD	NR CR UD	4.8 4.32 5.28	4.8 3.36 6.24	£9,313.07
Uncontrolled disease utility		0.67	0.75 0.58	£14,403.65 £5,799.96
IV wastage		None	100%	£9,953.71
% of IV pulse therapy		72%	33% 50% 100%	£12,752.52 £10,917.91 £5,521.96
Patient mean weight		67kg	87kg	£12,617.52
Number of RTX infusions		4	2	£5,569.76
Frequency of consultant visits (per cycle)		As per section **Error! Reference source not found.**	+50% -50%	RTX dominates £22,176.11

NR, non-remitters; CR, complete-response; UD, uncontrolled disease

Scenario Analysis

Table 6: Scenario analysis results

Parameter/attribute	Base Case	Tested values	ICER
Number of CYC courses	SoC – 2 Intervention – 1	SoC – 1 Intervention – 0	£23,633.55
		SoC – 2 Intervention – 0	RTX dominated
		SoC – 2 Intervention – 2	RTX dominates
		SoC – 1 Intervention – 1	RTX dominates
Which patients are offered a second course of RTX?	Non-remitters	No patients	£7,197.34
		Relapsing patients only	£9,502.83
		All patients	£9,663.61

Table 7: Subgroup analysis results

Subgroup	Number of CYC courses	ICER	Discussion
Newly diagnosed patients	SoC – 2 Intervention – 1	£55,174.92	Base case # of CYC cycles
	SoC – 2 Intervention – 2	£1,273.92	More plausible # of CYC cycles for this subgroup
Relapsing patients	SoC – 2 Intervention – 1	£43,003.05	Base case # of CYC cycles
	SoC – 0 Intervention – 0	£12,556.29	More plausible # of CYC cycles for this subgroup

Subgroup CYC intolerant

Table 8: CYC intolerant subgroup analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) incremental (QALYs)
RTX	£102,721	11.77	8.02	-£4,885	0.1387	0.5386	
BSC	£97,836	11.63	7.49				RTX dominates

Probability Sensitivity Analysis

Figure 3:Cost-effectiveness plane (updated PSA - varying utility of uncontrolled disease)

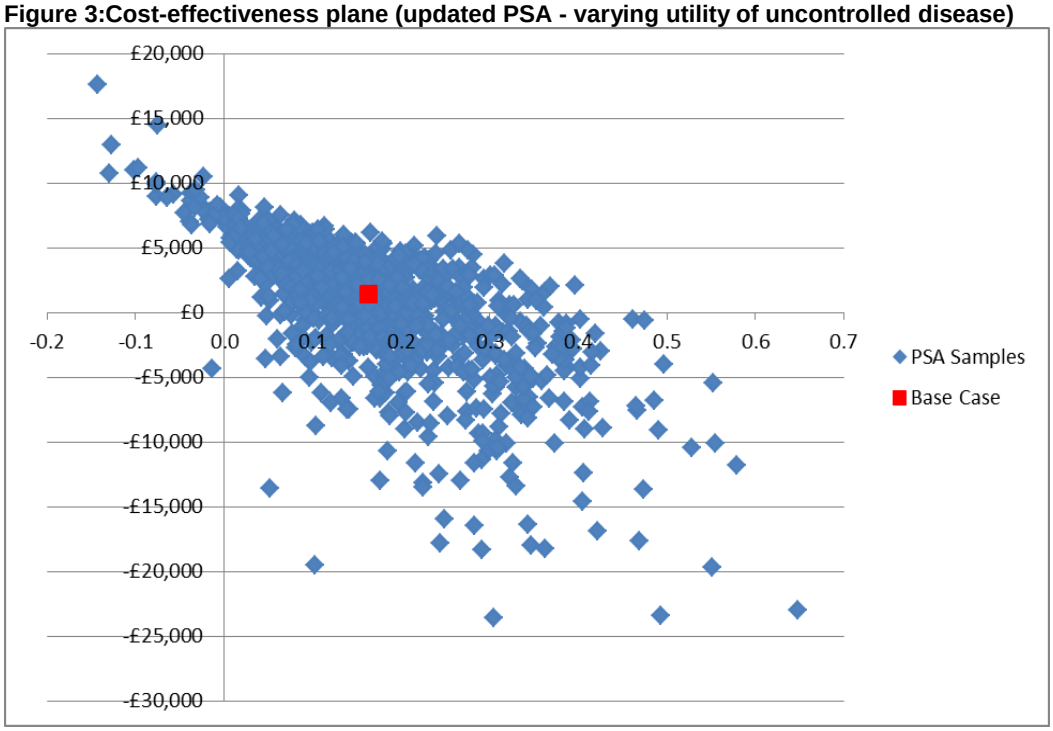
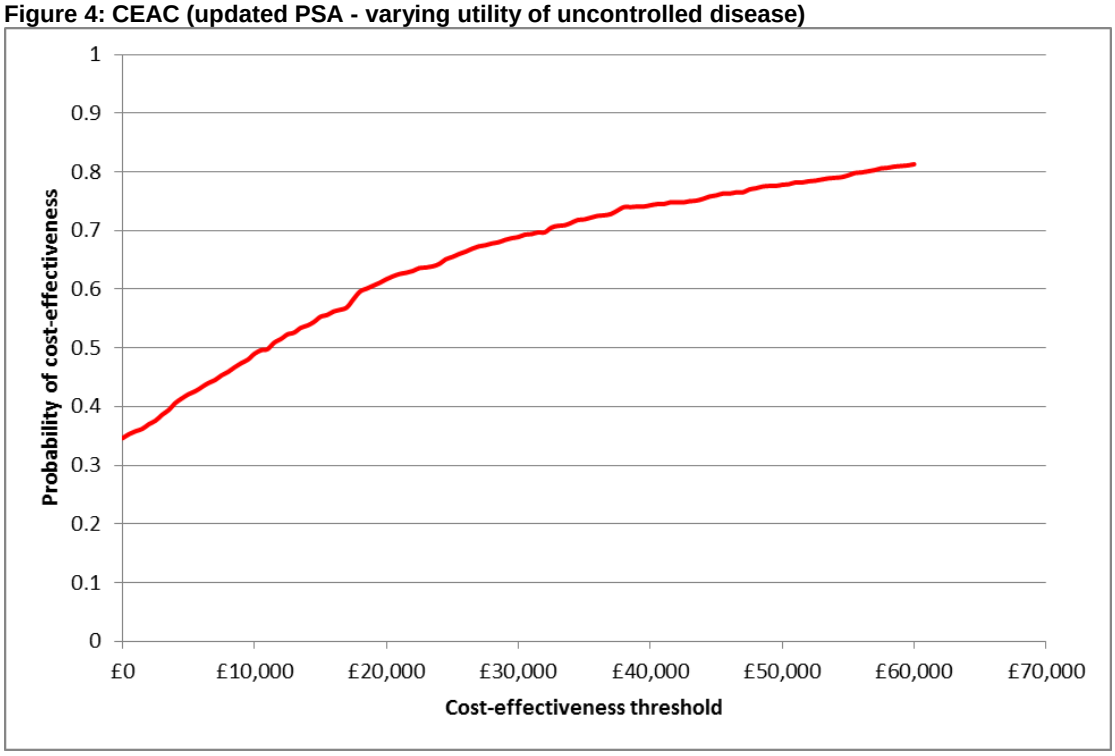


Figure 4: CEAC (updated PSA - varying utility of uncontrolled disease)



Appendix

1. PRISMA flow diagram
2. Justification of 45 publications excluded
3. Justification for exclusion criteria in the clinical search strategy
4. Non-RCT trials summary
5. Checklist of Items for Reporting Non-inferiority or Equivalence Trials
6. Anomalies in the clinical data from RAVE

PRISMA Flow Diagram

Figure 5:PRISMA flow diagram search screening

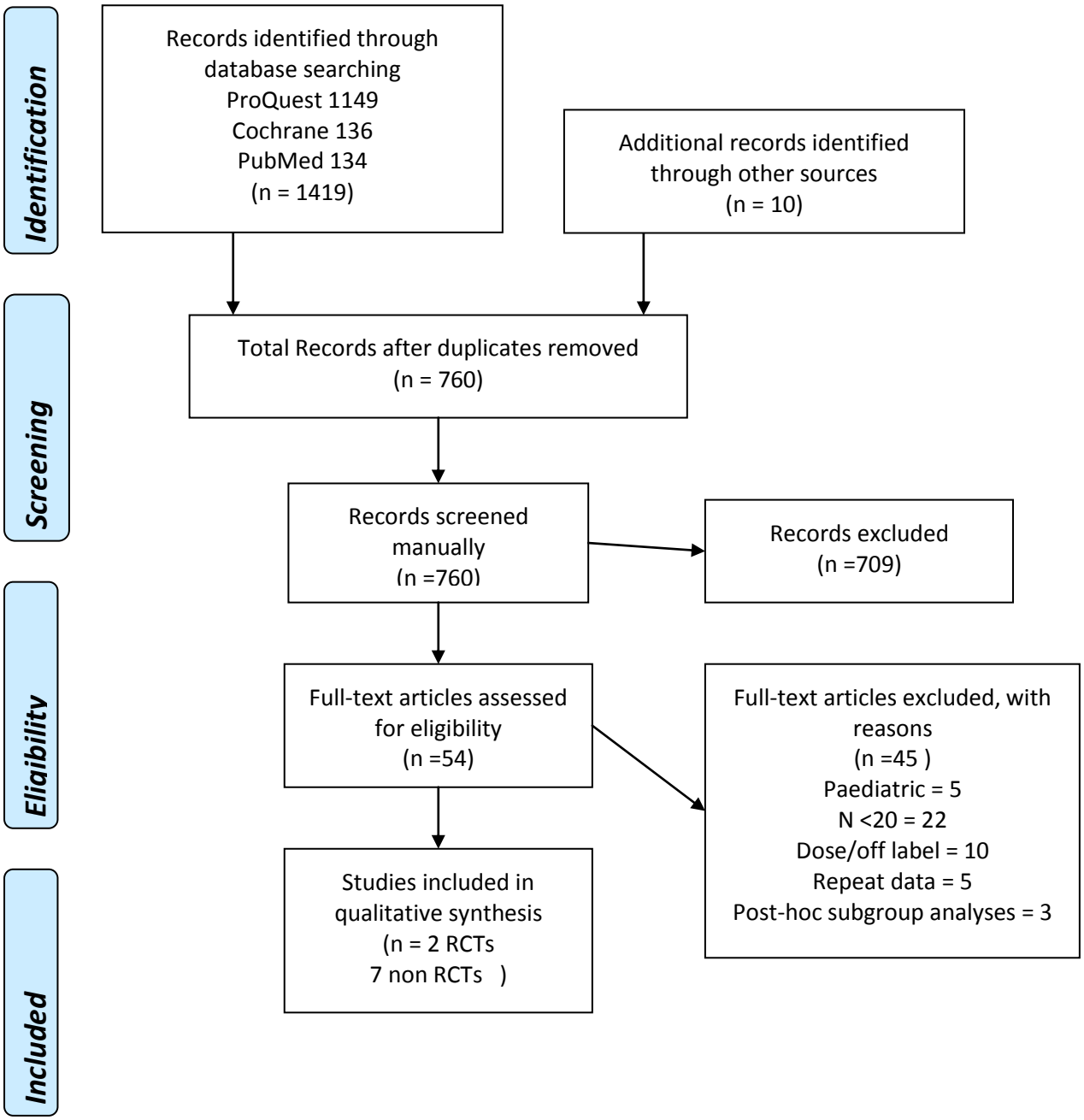


Table 9: 45 publications excluded (with justification) from PRISMA flow diagram

Study	Reference	Author	Reason for exclusion from STA
Successful use of rituximab for treatment of refractory paediatric granulomatosis with polyangiitis	Indian Journal of Rheumatology, suppl. 1 7 (Nov 2012): S52-S53.	Vishnu Vardhan Reddy et al.	Paediatric study
Open label study for treatment of pediatric Wegener's Granulomatosis with rituximab	Journal of Rheumatology, suppl. SUPPL. 2 37. 6 (Jun 2010): 1290.	Hutchinson et al.	Paediatric study
Single center experience with rituximab: Indications, use, and response in pediatric patients	Blood Purification 33. 1-3 (Mar 2012): 214.	George et al.	Paediatric study
Rituximab treatment for antineutrophil cytoplasmic antibody-associated vasculitis in children	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S1099.	Moore et al.	Paediatric study
Rituximab for severe disease flares in childhood ANCA vasculitides	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S124-S125.	Twilt et al.	Paediatric study
Rituximab induced remission of ANCA-associated scleritis: Two case studies	Rheumatology, suppl. SUPPL. 1 48 (Apr 2009): i122	Skeoch et al.	N<20 patients
Failure of rituximab monotherapy to control ANCA associated vasculitis - Case report	APMIS, suppl. SUPPL. 127 117 (Jun 2009): 100.	Rhee et al.	N<20 patients
Rituximab in ANCA-associated Vasculitis (AAV), a case series	APMIS, suppl. SUPPL. 127 117 (Jun 2009): 80.	Wendt et al.	N<20 patients
Rituximab is beneficial and safe in treatment of persistent pulmonary nodules in wegener's granulomatosis	American Journal of Respiratory and Critical Care Medicine, suppl. Meeting Abstracts 181. 1 (May 1, 2010).	Copley et al.	N<20 patients
Rituximab in the management of refractory neurological manifestations of wegener's granulomatosis: A case report	Rheumatology, suppl. SUPPL. 3 50 (Apr 2011): iii45-iii46.	Lutalo et al.	N<20 patients
Use of rituximab in refractory wegener's granulomatosis: Report of six cases	Italian Journal of Medicine, suppl. 1 5. 2 (Jun 2011): 82-83.	Paglione et al.	N<20 patients
Late recovery of renal function by rituximab in a patient with Wegener	Pediatric Nephrology 26. 9 (Sep 2011): 1625.	Malina et al.	N<20 patients

granulomatosis			
Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis in the autoimmunity and rituximab registry	Arthritis and Rheumatism, suppl. SUPPL. 1 63. 10 (Oct 2011).	Puechal et al.	N<20 patients
Crohn's disease or Wegener's granulomatosis or both?	American Journal of Gastroenterology, suppl. SUPPL. 1 107 (Oct 2012): S484.	Sharma et al.	N<20 patients
Rituximab in relapsing granulomatosis with polyangiitis (wegener's granulomatosis): A case series	Arthritis and Rheumatism, suppl. SUPPL. 1 63. 10 (Oct 2011).	Lutalo et al.	N<20 patients
Rituximab: rescue therapy in life-threatening complications or refractory autoimmune diseases: a single center experience	Rheumatology International (2012): 1-10.	Braun-Moscovici et al.	N<20 patients
Late recovery of renal function by rituximab in a patient with Wegener's granulomatosis	Pediatric Nephrology (2012): 1-4.	Malina et al.	N<20 patients
Adolescent female with thrombotic thrombocytopenic purpura associated with microscopic polyangiitis effectively treated with rituximab therapy	Blood Purification 33. 1-3 (Mar 2012): 212.	De Jesus-Gonzalez et al.	N<20 patients
Remission of resistant life-threatening non-renal wegener's granulomatosis with rituximab and mycophenolate mofitil	Rheumatology (United Kingdom), suppl. SUPPL. 3 51 (May 2012): iii154.	Heaney et al.	N<20 patients
Markers of T cell activation increase after rituximab administration in anca-associated vasculitis	Nephrology Dialysis Transplantation, suppl. SUPPL. 2 27 (May 2012): ii417.	Chocova et al.	N<20 patients
A difficult case of Wegener granulomatosis treated successfully with Rituximab	International Journal of Rheumatic Diseases, suppl. SUPPL. 1 15 (Sep 2012): 157.	Hamoun et al.	N<20 patients
Rituximab is an effective and safe treatment for treatment of refractory ANCA positive vasculitis-a single centre experience of six cases	International Journal of Rheumatic Diseases, suppl. SUPPL. 1 15 (Sep 2012): 110.	Khan et al.	N<20 patients

Crohn's disease or Wegener's granulomatosis or both?	American Journal of Gastroenterology, suppl. SUPPL. 1 107 (Oct 2012): S484.	Sharma et al.	N<20 patients
Successful treatment of eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome) with rituximab in a case refractory to glucocorticoids, cyclophosphamide, and IVIG	Modern Rheumatology (2012): 1-4.	Umezawa et al.	N<20 patients
Rituximab in the treatment of cyclophosphamide resistant ocular manifestations of Wegener's granulomatosis	Indian Journal of Rheumatology, suppl. SUPPL. 1 6. 3 (Nov 2011): S15.	Sasidharan et al.	N<20 patients
Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment	Arthritis and rheumatism 2006 Sep;54(9):2970-82.	Smith et al.	N<20 for AAV patients
Long-term follow-up of refractory systemic vasculitis treated with rituximab.	Rheumatology 2010 Apr;49:-i123.	Yazdani and Lanyon	N<20 patients
Rituximab as induction and maintenance therapies for ancaassociated vasculitis: A multicenter retrospective study on 80 patients	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S1004.	Charles et al.	Incorrect Licence/dose
Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S706.	Guillevin et al.	Incorrect Licence/dose
Long-term outcome of patients with granulomatosis with polyangiitis (wegener's) treated with rituximab	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S660-S661.	Azar et al.	Incorrect Licence/dose
Rituximab and leflunomide for	APMIS, suppl. SUPPL. 127 117 (Jun 2009):	Henes et al.	Incorrect Licence/dose

Wegener's granulomatosis: A long time follow-up	79.		
Efficacy of chronic pre-emptive rituximab treatment in ANCA-associated vasculitis	Scandinavian Journal of Rheumatology, suppl. SUPPL. 126 41 (2012): 41-42.	Besada et al.	Incorrect Licence/dose
Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis	Arthritis and Rheumatism 60. 5 (May 2009): 1540-1547.	Taylor et al.	Incorrect Licence/dose
Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis	Journal of Rheumatology 39. 1 (Jan 2012): 125-130.	Roubaud-Baudron et al.	Incorrect Licence/dose
A randomized controlled trial of Rituximab for the treatment of severe cryoglobulinemic vasculitis	Arthritis and Rheumatism 2012; 64 (3): 835-42	De Vita et al.	Incorrect Licence/dose
Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis	Nephrol Dial Transplant 2011;26 (10): 3280-6	Mansfield et al.	Incorrect Licence/dose
B cell depletion by rituximab severely reduces immunoglobulin levels in patients with anca-associated vasculitis previously treated with cyclophosphamide	Arthritis and Rheumatism, suppl. SUPPL. 1 63. 10 (Oct 2011).	Thie et al.	No dose given
Extended follow-up of treatment with rituximab versus cyclophosphamide for remission-induction of anca-associated vasculitis: Which subsets are at greatest risk for flare?	Arthritis and Rheumatism, suppl. SUPPL. 1 63. 10 (Oct 2011).	Stone et al.	Posthoc analysis of Subgroup
Immunoglobulin concentrations and infection risk among patients with ANCA-associated vasculitis treated with rituximab or cyclophosphamide	Arthritis and Rheumatism, suppl. SUPPL. 1 63. 10 (Oct 2011).	Specks et al.	Posthoc analysis of Subgroup
The efficacy of rituximab vs cyclophosphamide for treatment of renal	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S660.	Geetha et al.	Posthoc analysis of Subgroup

disease in anca-associated vasculitis: The rave trial geetha D, fervenza FC for the rave-itn research group			
Rituximab for ANCA-associated vasculitis: A meta-analysis of randomized trials	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S660.	Mejia et al.	Repeat data
Cyclovas: A rituximab (RTX)-based cyclophosphamide (CYP)-sparing regime	APMIS 2009 Jun;117:69-70.	Mansfield et al.	Repeat data (preliminary abstract)
Primary endpoint failure in the rituximab in ANCA-associated vasculitis trial	Arthritis and Rheumatism, suppl. 10 64 (Oct 2012): S707.	Miloslavsky et al.	Repeat data/no data/ subgroup
Rituximab for remission induction and maintenance in ANCA-associated vasculitis: A single-center ten-year experience in 108 patients	Arthritis and rheumatism 2010;62:S680	Cartin-Ceba et al.	Repeat data (preliminary abstract)
Rituximab versus cyclophosphamide in ANCA associated renal vasculitis	Nephrology 2010 Sep;15:49.	Peh et al.	Repeat data (preliminary abstract)

Table 10: Justification for exclusion criteria in the clinical search strategy

Exclusion criterion	Rationale
Any papers providing a review, update or commentary on data published elsewhere were excluded	To ensure no duplication of results/data only primary publications were included
Any papers which only mentioned RTX within a discussion of treatments for AAV or other auto-immune diseases were excluded	These papers did not include data, but concentrated on discussion/opinion on the use of RTX in AAV.
Papers covering the use of RTX Churg-Strauss syndrome were excluded	Churg-Strauss syndrome is not included in the licence for RTX in AAV, so use of RTX in Churg-Strauss is not considered pertinent to the decision problem
Animal studies or in vitro research	Only human data are considered relevant to the decision problem
Case reports	Single case studies may not be representative of the general clinical situation and are often published as they are “unusual”
Studies where there were data for fewer than 20 patients	With smaller sample sizes (n < 20), statistical tests lack power and may be misleading
Paediatric studies	Paediatric patients are not included in the licence for RTX in AAV, so use of RTX in paediatrics is not considered pertinent to the decision problem
Incorrect dosage	Only the licensed dose is considered pertinent to the decision problem
Maintenance of remission only	Only the licensed place in therapy is considered pertinent to the decision problem
Posthoc subgroup analyses	Not statistically robust analyses

Table 11: Non-RCT trials summary

Trial	Primary study ref.	Why was the study excluded?
Fixed interval RTX re-treatment. Retrospective data collection	Smith et al. Arth Rheum 2012 Accepted article doi:10.1002/art.34583	2 arms to the study. One arm allowed fixed retreatment with RTX every 6 months (outside of licence). The second arm consisted of 28 patients receiving either the licensed dose (375mg/m^2) or 1g x2 at a two week interval. However, these patients' results could not be distinguished from each other, hence data could not be used.
RTX survey, Retrospective data collection	Jones et al., Arth Rheum 2009; 60: 2156-2168	This was a retrospective survey and reported dosages and concomitant medications were unclear. 26 patients received the licensed dose of RTX (375mg/m^2) and 32 received two infusions, 1 g each given 2 weeks apart. 7 patients received other (not stated) doses. In addition to RTX, 28 patients received IV CYC, another 8 patients had stopped taking CYC just prior to initiation of RTX. No additional therapy was administered to 22 patients. These regimens were thought to be too heterogeneous to make any useful comparisons for the decision problem.
Protocolised RTX treatment	Jones et al., Arth Rheum 2010, 62; Suppl. Abstract	72 patients received a protocolised RTX regimen; 1g ×2 followed by 1g ×1 every 6 months for 2 years (5g total) with early immunosuppression and corticosteroid withdrawal. 34 received non-protocolised RTX; either 1g×2 or 375mg/m^2×4 only repeated if relapse occurred (results not separated by dose). These regimens were mostly off-label and thought to be too heterogeneous to make any useful comparisons for the decision problem.
Wegener's granulomatosis cohort study. Retrospective case note review	Del Pero et al., Clin Otolaryngol 2009; 34: 328-335	Only 14 patients received 375 mg/m^2 weekly for 4 weeks; the subsequent 20 received two doses of 1000 mg 2 weeks apart. N<20 for the RTX cohort, and the patients' results could not be distinguished from each other, hence data could not be used
RTX for remission induction and maintenance in WG - single centre observational 10 year experience	Cartin-Ceba et al., Arth Rheum 2012. Accepted article doi: 10.1002/art.34584	The RTX regimen consisted of 375 mg/m^2 of body surface area weekly for 4 weeks or two doses of 1g IV, 2 weeks apart. Patients' results could not be distinguished from each other, hence data could not be used.
RTX efficacy and safety in granulomatous vs vasculitic GPA. Retrospective data collection	Holle et al., Ann Rheum Dis 2012; 71: 327 – 333	All patients on licensed dose of RTX (375 mg/m^2 of body surface area weekly for 4 weeks) but publication suggests they were all also taking concomitant oral or IV CYC, which may have confounded comparison with RTX
GRAID (German Registry)	Roll et al., J Rheumatol 2012; 39: 2153-2156	RTX was given twice at a dosage of 1 g two weeks apart (n = 27) or as 4 weekly infusions of 375 mg/m^2 (n = 31). Patients' results could not be distinguished from each other, hence data could not be used.
Retrospective Long-Term Follow-Up from	Pullerits et al Scand J Immunology, 2012, 76, 411–420	RTX was added to on-going immunosuppressive treatment in 29 patients with refractory AAV, ie publication suggests all patients were also taking concomitant CYC or other

a Single Centre		immunosuppressive agents, which may have confounded comparison with RTX

Table 12: Checklist of Items for Reporting Non-inferiority or Equivalence Trials

Paper Section and Topic	Item Number	Descriptor (Adapted for Noninferiority or Equivalence Trials)	Any additional information based on Piaggio et al. checklist
Title and abstract	1*	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned"), *specifying that the trial is a noninferiority or equivalence trial.*	Roche believe this information was included in the original checklist
Introduction • Background	2*	Scientific background and explanation of rationale, *including the rationale for using a noninferiority or equivalence design*.	The design of RAVE was discussed with the US Food and Drug Administration (FDA) prior to study start, and was deemed to adequately address the proposed variation to the indication for rituximab. Thus the design and results of RAVE are in accordance with the criteria for establishing efficacy within a single trial as described, for example, in the U.S. FDA Guidance [FDA 1998: and EMA Points to consider [CPMP/EWP/2330/99: and are consistent with guidance on non-inferiority clinical trials [FDA 2010, EMEA/CPMP/EWP/2158/99]. These criteria were met and include the demonstration of a significant treatment effect on a clinically meaningful outcome of remission in a disease associated with high morbidity and mortality, statistically persuasive results for non-inferiority against an active control and for superiority to historical control, a multicentre study design, and consistency of results across subsets and across endpoints measuring different events.
Methods	3*	Eligibility criteria	Roche believe most of this

• Participants		for participants *(detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment)* and the settings and locations where the data were collected.	information was included in the original checklist. Participants were similar to those in trials established to determine efficacy of CYC in AAV
Interventions	4*	Precise details of the interventions intended for each group, *detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered.	Roche believe this information was included in the original checklist
Objectives	5*	Specific objectives and hypotheses, *including the hypothesis concerning noninferiority or equivalence.*	Roche believe this information was included in the original checklist
Outcomes	6*	Clearly defined primary and secondary outcome measures, *detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and,	Roche believe this information was included in the original checklist

		when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	
Sample size	7*	How sample size was determined, *detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules *(and whether related to a noninferiority or equivalence hypothesis)*.	Roche believe this information was included in the original checklist
Randomization Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	Roche believe this information was included in the original checklist
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	Roche believe this information was included in the original checklist
Implementation	10	Who generated the allocation sequence, who enrolled participants, and	Roche believe this information was included in the original checklist

		who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	Roche believe this information was included in the original checklist
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s), *specifying whether a 1- or 2-sided confidence interval approach was used*. Methods for additional analyses, such as subgroup analyses and adjusted analyses.	Roche believe this information was included in the original checklist
Results • Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.	Roche believe this information was included in the STA submission
Recruitment	14	Dates defining the periods of recruitment and	Roche believe this information was included in the STA submission

		follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	Roche believe this information was included in the STA submission
Numbers analyzed	16*	Number of participants (denominator) in each group included in each analysis and whether *"intention-to-treat" and/or alternative analyses were conducted*. State the results in absolute numbers when feasible (eg, 10/20, not 50%).	Roche believe this information was included in the STA submission
Outcomes and estimation	17*	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). *For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*	Roche believe this information was included in the STA submission
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	Roche believe this information was included in the STA submission
Adverse events	19	All important	Roche believe this information

		adverse events or side effects in each intervention group.	was included in the STA submission
Comment • Interpretation	20*	Interpretation of the results, taking into account the *noninferiority or equivalence hypothesis and any other* trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	Roche believe this information was included in the STA submission
Generalizability	21	Generalizability (external validity) of the trial findings.	Roche believe this information was included in the STA submission
Overall evidence	22	General interpretation of the results in the context of current evidence.	Roche believe this information was included in the STA submission

Table 13: Clinical Anomalies in RAVE

	Initial database lock	Updated data after hard-coding
Patient disposition: number of patients completed 18M visit as randomised in CYC group	62	63
Complete remission at 12 M		
RTX observed case	44 (44.4%)	47 (47.5%)
RTX worst case imputation	44 (44.5%)	47 (47.5%)
CYC observed case	37 (38.1%)	38 (38.8%)
CYC worst case imputation	37 (37.8%)	38 (38.8%)
P value (observed)	0.249	0.193
P value (worst case)	0.308	0.193
Complete remission at 18 M		
RTX observed case	38 (38.8%)	39 (39.4%)
RTX worst case imputation	38 (38.4%)	39 (39.4%)
CYC observed case	30 (31.3%)	32 (33.0%)
CYC worst case imputation	30 (30.6%)	32 (32.7%)
P value (observed)	0.248	0.322
P value (worst case)	0.229	0.297
BVAS=0 with prednisone <10mg/day at 12 M		
RTX observed case	55(82.1%)	59 (83.1%)
RTX worst case imputation	55 (55.6%)	59 (59.6%)
CYC observed case	57 (90.5%)	60 (61.2%)
CYC worst case imputation	57 (58.2%)	60 (61.2%)
P value (observed)	0.166	0.176
P value (worst case)		
BVAS=0 with prednisone <10mg/day at 18 M		
RTX observed case	53 (89.8%)	54 (90.0%)
RTX worst case imputation	53 (53.5%)	54 (54.5%)
CYC observed case	50 (84.7%)	52 (85.2%)
CYC worst case imputation	50 (51.0%)	52 (53.1%)
P value (observed)	0.166	0.176
P value (worst case)	0.407	0.428