NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

- Patients in RAVE and RITUXVAS who received rituximab and experience remission did not receive any maintenance treatment. The ERG's clinical specialists advised that they would expect maintenance treatment to be given in UK clinical practice to prevent disease relapse. Does Committee find it clinically plausible that no maintenance treatment would be given after using rituximab as induction therapy?
- The manufacturer explained that it did not provide evidence for rituximab compared with comparators other than cyclophosphamide in its submission because these would not be used to treat severe ANCA-associated vasculitis in clinical practice. The ERG's clinical advisers disagreed with this approach and indicated that rituximab and cyclophosphamide were not the only treatment options for this patient population, and especially for patients who cannot tolerate cyclophosphamide. The ERG identified some trials evaluating some of the comparators listed in the decision problem that could have enabled an indirect comparison. Does the Committee consider that including cyclophosphamide as the only comparator in the submission is appropriate?

- In the comparator arms of the 2 trials in the manufacturer's submission, cyclophosphamide was administered orally in RAVE and intravenously in RITUXVAS. The ERG noted that guidelines recommend both routes, and state that, although it may also be associated with a higher relapse rate, intravenous treatment produce higher remission rates and lower risk of side effects. What is Committee's view on how cyclophosphamide is administered in UK clinical practice?
- The manufacturer has primarily defined severe ANCA-associated vasculitis according to RAVE inclusion criteria. The ERG notes that this is more aligned with generalised disease defined in treatment guidelines, and that the manufacturer's submission does not provide evidence for all patients with severe ANCA-associated vasculitis. What is Committee's view on defining severe disease, bearing in mind the anticipated wording of the European marketing authorisation?
- In addition to the full trial populations with severe ANCA-associated vasculitis, the manufacturer has provided data for subgroups with newly diagnosed disease and those with relapsed disease. What is Committee's view on rituximab's clinical effectiveness in each of these populations?
- Consultees have described the adverse events associated with cyclophosphamide, including long-term toxicities such as infertility and increased risk of malignancy. The manufacturer noted that overall safety at 6 months and 18 months was comparable between rituximab and cyclophosphamide. How does Committee view the safety profile of rituximab compared with cyclophosphamide?

Cost effectiveness

- The ERG expressed concerns about the treatment pathway used in the manufacturer's model and noted that not all relevant treatment sequences had been included:
  - The range of comparators did not meet the decision problem
  - No maintenance treatment was given after induction therapy with rituximab
  - It would be unlikely that patients who did not respond to an initial course of rituximab would receive a second course (because of a lack of evidence)

  - Rituximab was investigated only as the first induction treatment received in the model, which did not allow a full incremental analysis
  - The proportion of patients receiving oral rather than intravenous cyclophosphamide was considered by the ERG to be too high

  What is Committee's view of the clinical plausibility of the treatment pathway used by the manufacturer in its economic model?

- The manufacturer considered that the average weight and body surface area for patients in RAVE (who were from the USA and the Netherlands) were not representative of the UK population with severe ANCA-associated vasculitis and used lower values. In several exploratory analyses, the ERG adjusted the values used by the manufacturer according to RAVE and also used values from a small study of UK patients, and noted that these were a key driver of the model. What does Committee consider to be the most appropriate values for weight and body surface area to be included in the economic model?
- The manufacturer did not differentiate between major and minor flares in its economic model because it believed that minor flares would generally evolve into major flares and require retreatment with induction therapy. The ERG's clinical advisers noted that it was often possible to control minor relapses with small adjustments to maintenance treatment, rather than starting induction therapy again. What is Committee's view on how relapses have been modelled by the manufacturer?
- The ERG had concerns about the uncontrolled disease health state because it believed that the costs were too high and the utility value assigned by the manufacturer was too low. It also found that patients entered this health state inappropriately quickly. What is Committee's view on how the uncontrolled disease health state has been modelled by the manufacturer?
- Does the Committee accept the ERG's exploratory analyses, including the adjustments to the model parameters? Which ICER does it consider to be the most plausible?

Other considerations

- The manufacturer noted that cyclophosphamide reduces fertility in men and women, and highlighted that the benefit of maintaining fertility while treating the disease effectively cannot be captured in the quality-adjusted life year (QALY). Does Committee consider that rituximab has demonstrated benefit in this regards?
- Are there any equality issues that Committee should consider when formulating its recommendations on rituximab for treating ANCA-associated vasculitis?

1 Background: clinical need and practice

1.1 Systemic vasculitis is an autoimmune condition characterised by damage to and inflammation of blood vessels and is often associated with anti-neutrophil cytoplasmic antibodies (ANCAs). ANCA-associated vasculitis is an umbrella term for several related conditions, including microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's granulomatosis). ANCA-associated vasculitis mostly affects small and medium sized blood vessels, particularly those in the respiratory and renal systems. One of the primary mediators of ANCA-associated vasculitis pathology is thought to be B-lymphocytes, but the precise mechanism is unknown.

1.2 It is estimated that around 1200 people are diagnosed with ANCA-associated vasculitis each year in England and Wales. The annual UK incidence of microscopic polyangiitis and granulomatosis with polyangiitis is estimated to be between 6 and 11 per million population. The incidence of ANCA-associated vasculitis increases with age and the peak age of onset is 60–70 years.

1.3 The aim of treatment is initially to induce remission, then to maintain remission and treat relapse when necessary. Without treatment, the condition is fatal and the 1-year mortality for ANCA-associated vasculitis is 11% (because of complications of vasculitis and infection). Clinical management has been largely based on cyclophosphamide, along with

corticosteroids (for example, prednisolone). Cyclophosphamide is standard treatment for inducing remission, and is given for 3–6 months. Around 15% of people taking cyclophosphamide do not experience remission but continue to have active or progressive refractory disease. Adverse effects of cyclophosphamide include serious infection, infertility and haemorrhagic cystitis. Long-term use increases the risk of bladder cancer, lymphoma and non-melanoma skin cancer. Immunosuppressive drugs such as methotrexate, azathioprine, and mycophenolate may also be used as maintenance therapy. There is no related NICE guidance for the treatment of ANCA-associated vasculitis.

2 The technology

2.1 Rituximab (MabThera, Roche Products) is a genetically engineered chimeric (mouse/human) monoclonal antibody that depletes B cells by targeting cells bearing the CD20 surface marker. It does not currently have a European marketing authorisation for treating ANCA-associated vasculitis. The European Medicines Agency's Committee for Medicinal Products for Human Use has issued a positive opinion for rituximab in combination with glucocorticoids for 'the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)'. Rituximab has been studied in clinical trials in people with severe ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) compared with cyclophosphamide (in combination with methylprednisolone and prednisone) and with azathioprine (in combination with prednisolone).

2.2 In RAVE, common adverse events with an absolute increase in incidence of 5% or greater in the rituximab group over the cyclophosphamide group in the treatment of granulomatosis with polyangiitis and microscopic polyangiitis: diarrhoea, peripheral oedema, urinary tract infection and cough.

2.3 The anticipated recommended dosage of rituximab in combination with glucocorticoids for treating granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks. Rituximab is priced at £174.63 per 10 ml vial and £873.15 per 50 ml vial (excluding VAT; British national formulary [BNF] edition 65). The manufacturer's estimate of the average cost of a course of treatment is £4889.64 (based on 1.79 m^2 body surface area and no vial sharing). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids within its licensed indication for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with anti-neutrophil cytoplasmic antibody associated vasculitis	People with severe ANCA-associated vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis)

The manufacturer advised that the patient population addressed in the decision problem in its submission was in line with the anticipated European marketing authorisation for rituximab for treating ANCA-associated vasculitis. The ERG agreed the population specified by the manufacturer was appropriate, but noted that clinical advice to the ERG suggested people with other types of ANCA-associated vasculitis may receive rituximab in clinical practice, as well as certain categories of people with less severe disease (for example, women who wish to become pregnant). The ERG also noted that there is no clear-cut definition of severe disease, and that the clinical evidence submitted by the manufacturer did not encompass all types of severe disease.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Rituximab in combination with corticosteroids	Rituximab in combination with corticosteroids for induction treatment only

The manufacturer advised that the intervention specified in the decision problem in its submission was in line with the anticipated European marketing authorisation for rituximab for treating ANCA-associated vasculitis. The ERG acknowledged the scope of the anticipated European marketing authorisation but indicated that, according to clinical advice, it was unlikely that patients would not receive any maintenance treatment.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	Treatment strategies without rituximab, including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids)	Cyclophosphamide (in combination with corticosteroids) for induction of remission. Patients intolerant to cyclophosphamide may receive alternative induction treatments including azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids)

The manufacturer advised that it had received clinical opinion that cyclophosphamide is the standard of care in the induction of remission (except for patients intolerant to cyclophosphamide) and that other treatments are usually reserved for less severe forms of ANCA-associated vasculitis. Although the manufacturer acknowledged patients who cannot tolerate cyclophosphamide may receive alternative induction treatments, these were not included in the economic evaluation of this subgroup. The manufacturer added that there was no evidence of rituximab directly compared with other induction treatments in the target population. The ERG noted the absence of comparators other than cyclophosphamide. Although ERG agreed that cyclophosphamide was the most relevant comparator, it highlighted the importance of treatment sequencing because multiple relapses and remissions

are possible. The ERG noted that a plausible treatment sequence would be initial treatment with cyclophosphamide to induce remission then rituximab upon relapse to induce subsequent remission.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • mortality • remission rate and duration of remission • number and severity of relapses • change in renal function • cumulative dose of immunosuppressants • adverse effects of treatment • health-related quality of life	We have explored the following outcome measures based on the evidence available: • mortality • remission rate and duration of remission • relapse rates • cumulative dose of immunosuppressants • adverse effects of treatment • health-related quality of life

The manufacturer concluded that not all the outcomes outlined in the final scope could be included because of limitations in the evidence base. Although the RAVE study provided information on relapse rates, the manufacturer did not model the severity of individual relapses. The ERG viewed the outcomes presented in the clinical-effectiveness section of the manufacturer's submission to be appropriate but noted some of these outcomes (different severities of relapse and changes in renal function) had not been incorporated into the manufacturer's economic model. Clinical advice received by the ERG suggested that failing to model relapses of different severity could be important because this strongly influences treatment options and the disease pathway.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Same as the scope

3.2 The scope stated that, if evidence allowed, the subgroup of people for whom cyclophosphamide is contraindicated should be considered. In its submission, the manufacturer considered the following 3 subgroups:

- patients with de novo disease
- patients with prior exposure to cyclophosphamide
- patients for whom cyclophosphamide is contraindicated.

The manufacturer highlighted that the RAVE study included patients with either newly diagnosed or relapsing disease and reported significantly different outcomes based on prior exposure to cyclophosphamide. Because of limitations in the available evidence, the manufacturer did scenario analyses for patients considered intolerant to cyclophosphamide who were receiving alternative induction agents (azathioprine, methotrexate, and mycophenolate).

4 Clinical-effectiveness evidence

4.1 The manufacturer's systematic review identified 2 relevant randomised controlled trials for inclusion in its submission: RAVE and RITUXVAS

(table 1). Seven non-randomised controlled trials were identified but the manufacturer judged the data were insufficient to be useful to the decision problem. The manufacturer explained that its submission focused on efficacy data from the RAVE study and that these data were complemented by the RITUXVAS study results. Both RAVE and RITUXVAS compared rituximab with cyclophosphamide in patients with ANCA-associated vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis). RAVE recruited both newly diagnosed and relapsing patients, whereas RITUXVAS recruited newly diagnosed patients with renal involvement.

Table 1 Overview of randomised controlled trials included in the manufacturer's submission

Trial	Intervention	Comparator	Population
RAVE	Rituximab 375mg/m^2 x 4 weeks	Oral cyclophosphamide (2 mg/kg/day) followed by azathioprine	• Patients with severe active ANCA-associated vasculitis[a] • Newly diagnosed or relapsed disease
RITUXVAS	Rituximab 375mg/m^2 x 4 weeks + 2 cyclophosphamide intravenous pulses	Intravenous cyclophosphamide (15 mg/kg) followed by azathioprine	• Patients with active ANCA-associated vasculitis[a] • Renal involvement • Newly diagnosed disease

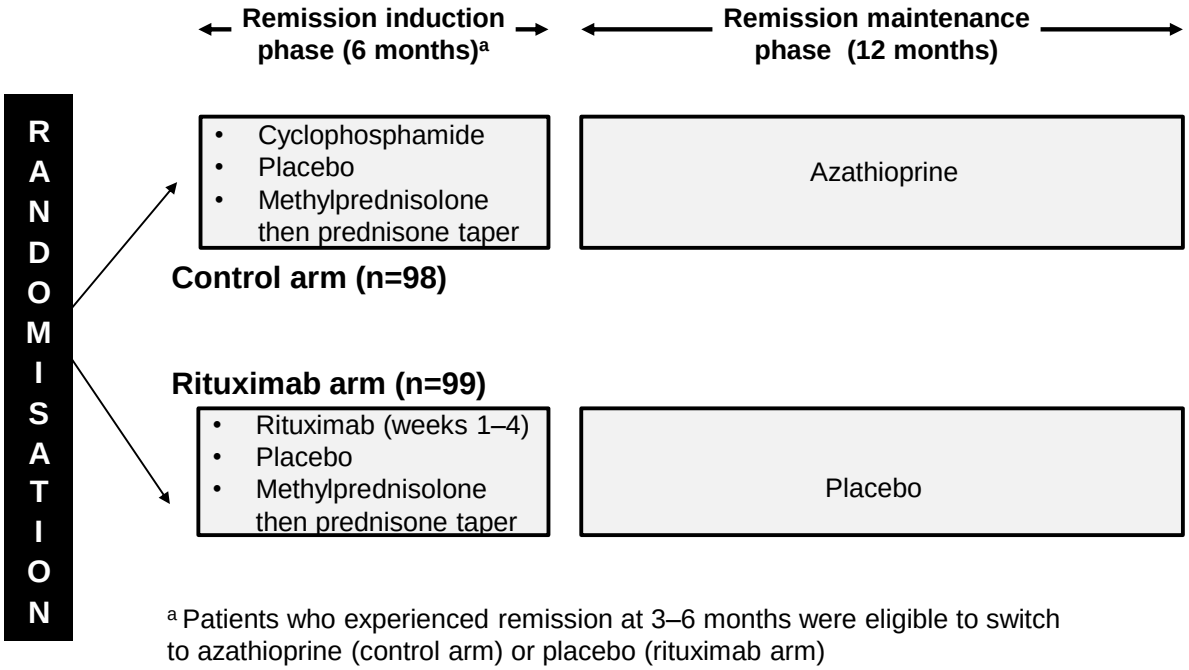
[a] Microscopic polyangiitis and granulomatosis with polyangiitis

RAVE study

4.2 The RAVE study was a randomised, multicentre, double-blind, double-dummy, placebo-controlled trial conducted in the USA and the Netherlands, which compared rituximab with conventional therapy (cyclophosphamide and azathioprine) in patients with severe ANCA-associated vasculitis. The study tested the hypothesis that rituximab was not inferior to conventional therapy in its ability to induce disease remission in ANCA-associated vasculitis at 6 months. Eligible patients had either granulomatosis with polyangiitis or microscopic polyangiitis, had tested positive for ANCA at screening, and had evidence of severe disease and a Birmingham Vasculitis Activity Score for Wegener's

Granulomatosis (BVAS/WG) of 3 or more. BVAS/WG scores range from 0 to 63, with higher scores indicating more active disease. A 6-month remission induction phase was followed by a 12-month remission maintenance phase (figure 1).

Figure 1 Summary of RAVE study design



[a] Patients who experienced remission at 3–6 months were eligible to switch to azathioprine (control arm) or placebo (rituximab arm)

4.3 At the start of the study, all patients received an intravenous glucocorticoid pulse (methylprednisolone 1 g, or equivalent dose of an alternative drug) followed by an oral prednisone taper (dose starting at 1 mg/kg/day and not exceeding 80 mg/day). Patients in the rituximab arm (n=99) received rituximab 375 mg/m^2 once weekly infusions for 4 weeks plus daily oral placebo and daily oral prednisone for 3–6 months to induce remission then switched to oral placebo as maintenance treatment until 18 months after starting induction treatment. Patients in the cyclophosphamide arm (n=98) received daily oral prednisone cyclophosphamide plus placebo infusions to induce remission then oral azathioprine 2 mg/kg/day as maintenance therapy until 18 months after starting induction treatment. In both groups, patients who experienced remission before 6 months of treatment were eligible to switch to maintenance treatment from month 4 onwards. The full publication stated

that patients who experienced a severe flare could cross over to the other treatment arm and receive the other induction regimen in full. Patients whose BVAS/WG had not decreased by at least 1 point at 1 month, or who had a new manifestation of disease were classified as having early treatment failure. These patients discontinued their assigned treatments and were treated according to best medical judgement.

4.4 The RAVE study's primary outcome was the induction of complete remission at 6 months, defined as a BVAS/WG of 0 and successful completion of the prednisone taper (that is, prednisone dose was 0 mg). A secondary analysis of the primary outcome assessed the superiority of rituximab to cyclophosphamide in patients who had complete remission at 6 months. Tertiary outcomes were cumulative BVAS/WG area under the curve for 6 months; BVAS/WG of 0 on prednisone less than 10 mg/day at 6 months; partial remission (BVAS/WG of 2 or less and no prednisone at 6 months); cumulative glucocorticoid dose at 6 months; number of severe flares at 6 months; number of limited flares at 6 months; and quality of life using Study 36-Item Short Form (SF-36) Physical Component Summary and Mental Component Summary scores. Additionally, the published study protocol stated that laboratory markers of inflammation (erythrocyte sedimentation rate and C-reactive protein) were measured. Disease damage was measured using the Vasculitis Damage Index (range 0–64, with higher scores indicating more severe damage). End points for the assessment of efficacy up to 18 months included duration of complete remission and time to limited and/or severe flare after complete remission.

4.5 Baseline demographic and disease characteristics in the RAVE study were generally similar between the treatment groups except for creatinine clearance, which was lower in the rituximab arm. Ninety-six (48.7%) patients were newly diagnosed at the time of screening. Eighty-two (83%) patients in the rituximab group and 79 (81%) patients in the cyclophosphamide group completed the 6-month remission induction phase without crossover or change to best medical judgement. A similar

proportion of patients in the 2 groups completed 18 months on randomised treatment (62% taking rituximab and 63% taking cyclophosphamide).

4.6 Sixty-three (64.3%) of the 98 patients in the rituximab arm experienced complete remission at 6 months compared with 52 (54.7%) of 95 patients in the cyclophosphamide arm (table 2). The absolute difference in rate of remission between the 2 groups was 9.5% (95% CI −4.30% to 23.40%). This showed the non-inferiority of rituximab to cyclophosphamide in the induction of complete remission because the lower limit of the 95% CI (−4.30%) was higher than the predetermined non-inferiority margin (−20%). After estimating missing data by worst case imputation, 63.6% of the 99 patients in the rituximab arm achieved complete remission at 6 months compared with 53.1% of the 98 patients in the cyclophosphamide arm (absolute treatment difference 10.6% [95% CI −3.18% to 24.33%]).

Table 2 RAVE primary outcome: complete remission at 6 months (ITT population)

	Rituximab (n=98)	Cyclophosphamide (n=95)	Absolute % difference in rate	95.1% CI of difference
Complete remission, n	63	52		
Complete remission, % (95% CI)	64.3 (54.8 to 73.8)	54.7 (44.7 to 64.8)	9.5	−4.3 to 23.4

CI, confidence interval; ITT, intention to treat. Percentages are based on the number of patients with non-missing results for complete remission at 6 months

Source: page 70 of the manufacturer's submission

4.7 The remission rate at 6 months in the rituximab arm was not statistically significantly superior to the cyclophosphamide arm (95% CI for the between-group difference −4.30% to 23.40%; p=0.177). The outcome was similar using the worst case imputation (95% CI for the between-group difference −3.2% to 24.3%; p=0.132). In a prespecified analysis, the manufacturer concluded that survival with rituximab was superior to expected survival rates for untreated patients using historical control data generated from a study by Walton et al., 1958, which described a cohort

of 56 largely untreated patients with granulomatosis with polyangiitis (see page 58 of the manufacturer's submission for details of the statistical assumptions and calculations).

4.8 A summary of the tertiary end points is given in table 3. There was no statistically significant difference between the treatment arms in cumulative BVAS/WG area under the curve during the first 6 months, remission on less than 10 mg/day prednisone at 6 months, partial remission, severe or limited flares, median cumulative dose of prednisone from randomisation to 6 months. In an exploratory analysis that investigated the rate of remission, regardless of prednisone use, there was a statistically significantly greater proportion of patients in the rituximab arm than in the cyclophosphamide arm who experienced a BVAS/WG of 0 (80.8% compared with 66.3%; p=0.021).

Table 3 RAVE efficacy results for tertiary end points (ITT population)

	Rituximab (n=99)	**Cyclophosphamide (n=98)**	**Absolute difference (95% CI)**	**p-value**
Tertiary end points				
% in remission on <10 mg/day of prednisone (95% CI)	70.7 (61.7, 79.7)	62.2 (52.6, 71.8)	8.5 (-4.7, 21.6)	0.208
% with severe flare	5.1	10.2		
Rate of severe flares per patient-month	0.011	0.019		0.293
% with limited flare	12.1	14.3		
Rate of limited flares per patient-month	0.026	0.026		0.98
Mean (SD) BVAS/WG AUC over first 6 months	1.29 (1.33)	1.25 (1.03)		
Median cumulative prednisone dose (1000 mg) (95% CI)	3.3 (1.0, 6.9)	3.5 (0.7, 8.3)		0.055
Mean change from baseline in ESR (95% CI)	-14.4 (-18.7, -10.1)	-9.3 (-15.6, -3.0)	7.6 (2.2, 13.1)	0.006
Mean change from baseline in CRP (95% CI)	-2.69 (-5.44, 0.06)	-2.84 (-7.07, 1.40)	0.61 (-0.5, 1.73)	0.278
Exploratory endpoint				
Patients (%) in remission (BVAS/WG=0) (95% CI)	80.8 (73.0, 88.6)	66.3 (60.0, 75.7)	14.5 (2.3, 26.7)	0.021

AUC,area under the curve; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's granulomatosis; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Source: page 34 of the ERG report

4.9 Quality-of-life scores improved in both groups; there was no significant difference between treatment arms in the change in quality-of-life scores

or their rate of change from baseline to 6 months. From baseline to 6 months, scores on the Vasculitis Damage Index increased by 1.3 points in the rituximab arm and 1.5 points in the cyclophosphamide arm (p=0.62).

4.10 The manufacturer explored the effects of various baseline characteristics in relation to the primary outcome including relapsing disease and renal disease. In patients who had relapsing disease at baseline, a statistically significantly higher proportion in the rituximab arm experienced complete remission at 6 months than in the cyclophosphamide arm (66.7% versus 42.0%, p=0.013). Complete remission rates in patients with new disease were similar in the 2 treatment arms (see table 4).

Table 4 Manufacturer's RAVE subgroup results: complete remission at 6 months for patients with new or relapsing disease at baseline

	Rituximab n/N (%)	**Cyclophosphamide n/N (%)**	**Absolute difference, % (95% CI)**	**p-value**
New disease at baseline	29/48 (60.4)	31/48 (64.6)	−4.2 (−23.6 to 15.3)	0.673
Relapsing disease at baseline	34/51 (66.7)	21/50 (42.0)	24.7 (5.8 to 43.6)	0.013

CI, confidence interval
Source: page 80 of the manufacturer's submission

4.11 The manufacturer presented results for a subgroup analysis according to renal disease at baseline (table 5). Complete remission rates in patients who had at least 1 major renal disease item at baseline (according to BVAS/WG assessment) were similar between the rituximab and cyclophosphamide arms (60.8% compared with 62.7%). Patients without a major renal disease item were statistically significantly more likely to experience complete remission in the rituximab arm compared with the cyclophosphamide arm (66.7% compared with 42.6%; p=0.018).

Table 5 Manufacturer's RAVE subgroup results: complete remission at 6 months for patients either with or without 1 major renal item on BVAS/WG at baseline

Patient group	Rituximab n/N (%)	Cyclophosphamide n/N (%)	Absolute difference, % (95% CI)	p-value
One major renal item on BVAS/WG	31/51 (60.8)	32/51 (62.7)	−2.0 (−20.9 to 17.0)	0.839
No major renal item on BVAS/WG	32/48 (66.7)	20/47 (42.6)	24.1 (4.69 to 43.6)	0.018

BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis;
CI, confidence interval
Source: page 80 of the manufacturer's submission

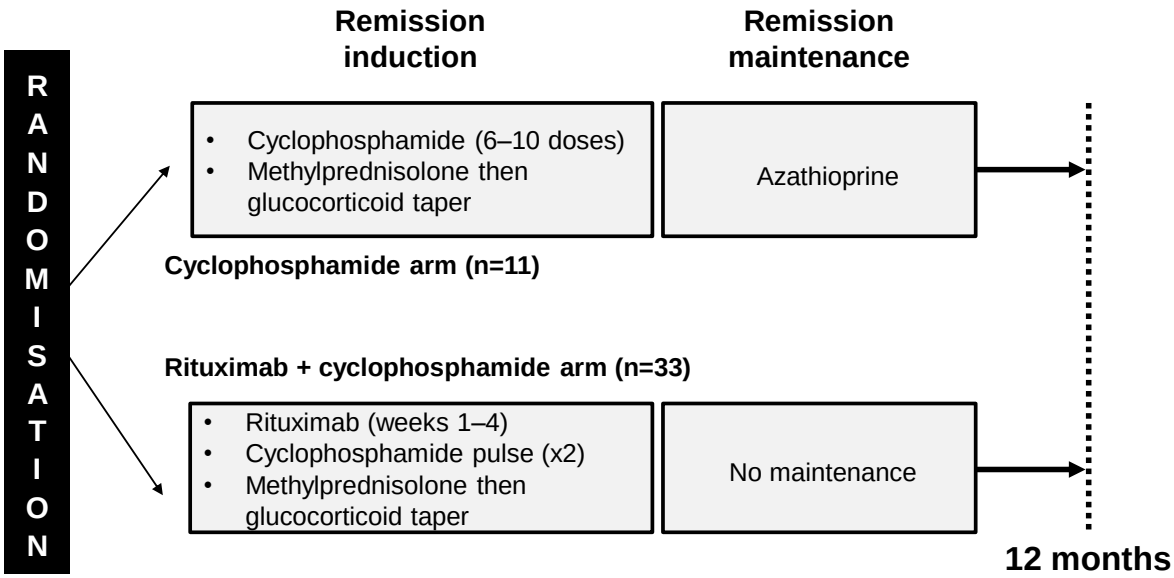
For the results of other subgroup analyses (alveolar haemorrhage at baseline, ANCA type at baseline and change in ANCA status from baseline), see pages 80–83 of the manufacturer's submission.

RITUXVAS study

4.12 The RITUXVAS study was a phase II, open-label, randomised, controlled trial conducted in Europe and Australia. It compared the efficacy and safety of rituximab plus cyclophosphamide as induction therapy with cyclophosphamide plus azathioprine in 44 patients with newly diagnosed, severe ANCA-associated vasculitis and renal involvement (figure 2). Patients were randomised to rituximab (n=33) or cyclophosphamide (n=11) and both arms received intravenous methylprednisolone (1 g) and an oral glucocorticoid (1 mg/kg/day initially, reducing to 5 mg/day at the end of 6 months). Patients in the rituximab arm received rituximab (375 mg/m^2 weekly, for 4 weeks), and intravenous cyclophosphamide (15 mg/kg with the first and third rituximab infusions). A further dose of intravenous cyclophosphamide (15 mg/kg) was permitted for patients who had progressive disease within the first 6 months. Patients in the rituximab arm did not receive azathioprine to maintain remission. Patients in the control arm received intravenous cyclophosphamide (15 mg/kg for 3–6 months [6–10 doses in total]), followed by azathioprine maintenance (2mg/kg/day). Further treatment with rituximab or cyclophosphamide was permitted in cases of relapse. The primary end points for RITUXVAS were

sustained remission at 12 months (defined as BVAS of 0 maintained for at least 6 months) and severe adverse events. Major secondary and tertiary end points were time to remission (BVAS = 0), BVAS area under the curve, change in glomerular filtration rate, prednisolone dose, and quality of life and disease damage (assessed by the SF-36 questionnaire and Vasculitis Damage Index between 0 and 12 months). Analyses were performed on an intention-to-treat basis.

Figure 2 Summary of RITUXVAS study design



4.13 There were no major imbalances in baseline characteristics between the 2 groups, except for a greater proportion of renal-limited vasculitis patients in the cyclophosphamide group and a greater proportion of patients requiring dialysis in the rituximab plus cyclophosphamide group. No patients were lost to follow-up. Sustained remission occurred in 76% of patients in the rituximab plus cyclophosphamide group and 82% of patients in the cyclophosphamide group (table 6). The absolute difference in sustained remission with rituximab plus cyclophosphamide compared with cyclophosphamide was −6% (95% confidence interval −33 to 21). Among patients who reached 12 months, 93% of patients in the rituximab plus cyclophosphamide group and 90% of patients in the cyclophosphamide group achieved sustained remission. Of the 9 patients

who were dependent on dialysis at study entry, 6 out of 8 patients in the rituximab plus cyclophosphamide group experienced sustained remission (5 of whom became dialysis independent) and the 1 patient from the cyclophosphamide group died shortly after study entry.

Table 6 RITUXVAS primary efficacy results (ITT population)

	Rituximab plus cyclophosphamide	Cyclophosphamide
Achieved sustained remission at 12 months, n (%)	25 (76)	9 (82)
Reasons for non-response		
Death, n (%)	6 (18)	1 (9)[a]
Relapse within 6 months after remission, n (%)	1 (4)	1 (9)
Re-treated for incomplete remission, n (%)	1 (4)	0

[a] Another patient died at 19 months, for a total of 2/11 (18%) deaths in the cyclophosphamide group
Source: page 85 of the manufacturer's submission

4.14 Remission (defined as BVAS of 0 for 2 months) occurred in 91% of patients in each of the treatment groups. As described in the full publication of the RITUXVAS study, there were no statistically significant differences between treatment groups in median time to remission (p=0.87), prednisolone dose at 12 months (p=0.78), median estimated glomerular filtration rate (p=0.14 for the comparison of medians), median change in the Vasculitis Damage Index (p=0.38) or physical composite SF-36 score (p=0.36). Median BVAS fell from 19 (interquartile range 14 to 24) at entry to 0 (interquartile range 0 to 1.5) at 3 months in the rituximab plus cyclophosphamide group and 18 (interquartile range 12 to 25) at entry to 0 (interquartile range 0 to 0) at 3 months in the cyclophosphamide group. Patients in the cyclophosphamide group had a statistically significantly better mental composite SF-36 score in comparison than the rituximab plus cyclophosphamide group (p=0.04) but excluding outlying data for 2 patients eliminated the statistical significance (p=0.32).

4.15 The manufacturer did not do any indirect comparisons or meta-analyses and advised that the economic evaluation was based solely on the RAVE study results. It stated that the RAVE study reflected the marketing

authorisation and scope of the appraisal, whereas the way rituximab was given in the RITUXVAS study was fundamentally different.

4.16 The manufacturer's submission described rituximab's safety profile using the Summary of Clinical Safety provided to the European Medicines Agency to support the marketing authorisation application for rituximab for treating severe ANCA-associated vasculitis. The Summary of Clinical Safety summarises exposure to rituximab in 99 patients with ANCA-associated vasculitis who were followed for 18 months as part of follow-up to RAVE. In addition, 33 patients in RITUXVAS were followed for up to 24 months, and 162 patients in other investigator-initiated studies were followed for between 3 and 55 months. An overview of the adverse events common to RAVE (assessed at 6 months) and RITUXVAS (assessed at 12 months) is given in table 7.

Table 7 Number of adverse events in any arm

Adverse events	RAVE (at 6 months)	RITUXVAS (at 12 months)
	Rituximab (n=99) / Cyclophosphamide (n=98)	Rituximab + cyclophosphamide (n=33) / Cyclophosphamide (n=11)
Serious adverse events (≥ grade 3)	31/12	73/85
Deaths	1/2	6/2 (both 18%)
Cancer (patients)	1/1†	2/0
All infections	NR	19/7
Serious infections (≥ grade 3)	7/7	7/3
Thrombocytopenia	3/1*	1/0
Neutropenia	NR	2/1
Leucopenia (≥ grade 2)	3/10	NR

*(≥grade 3) †5/2 for >6 months' follow-up
Source: page 35 of the ERG report

4.17 The manufacturer reported that overall safety at 6 months and 18 months was comparable between the rituximab and cyclophosphamide groups in RAVE, including the incidences and rates per patient-year of any adverse event, selected adverse events, adverse events that were grade 3 or higher, serious adverse events, and serious infections. The manufacturer stated that although the data are limited, safety in the other published studies was consistent with the RAVE study. Overall death rates and causes of death in RAVE and RITUXVAS were similar in the rituximab

and cyclophosphamide groups. The most commonly reported type of serious adverse event in all studies was infection, with similar incidences between rituximab and cyclophosphamide groups in the controlled studies. The incidences and rates of serious adverse events were comparable between the rituximab and cyclophosphamide groups in RAVE at 6 months (33.3% compared with 33.7%) and 18 months (46.5% compared with 41.8%), and in RITUXVAS at 12 months (42% compared with 36%). The full publication of RITUXVAS reported that there was no statistically significant difference between treatment groups in incidence rates of severe adverse events (p=0.77).

ERG critique of rituximab's clinical effectiveness

4.18 The ERG noted that restricting the systematic review of clinical – effectiveness studies to the population and intervention in the anticipated European marketing authorisation meant that it did not fulfil the scope or decision problem specified by NICE. The ERG did not identify any further randomised controlled trials directly comparing rituximab with the comparators in the NICE scope and decision problem in patients with ANCA-associated vasculitis. However, it did identify 5 ongoing or published trials that could potentially have enabled an indirect comparison or mixed treatment comparison of rituximab with comparators other than cyclophosphamide that were specified in the NICE scope and decision problem.

4.19 The ERG broadly agreed with the treatment pathway described by the manufacturer but noted some uncertainties:

- High cumulative dose of cyclophosphamide indicates increased risk of adverse events, and giving the drug intravenously rather than orally may offer the opportunity to reduce the cumulative dose, or allow more courses to be given. However, the ERG judged this to be inadequately highlighted by the manufacturer.

- The ERG was aware that the manufacturer's submission did not adequately consider alternative treatments to cyclophosphamide that may be used to induce remission.
- The ERG observed that the European Vasculitis Study Group guidelines recommend maintenance treatment after remission, and received clinical specialist advice that not receiving any maintenance treatment after remission with rituximab was an unrealistic treatment pathway. The ERG also noted that relapse is not inevitable with appropriate maintenance treatment.
- The 2 × 1000 mg dosage of rituximab is used more often in UK clinical practice to treat ANCA-associated vasculitis than the 4 × 375/mg^2 dosage that is anticipated to be recommended in the European marketing authorisation.

4.20 The ERG noted that the manufacturer's submission presented RAVE as the most relevant to the decision problem because it compared rituximab and cyclophosphamide using rituximab's anticipated recommended dosage for patients with generalised severe ANCA-associated vasculitis. However, clinical specialist advice to the ERG was that the rituximab regimen in RITUXVAS, which included 2–3 pulses of cyclophosphamide, was clinically relevant and should therefore be equally regarded because the 2 rituximab regimens have not been compared with each other.

4.21 The ERG stated that the evidence suggested that rituximab was superior to oral cyclophosphamide (p=0.01) in the subgroup of patients with relapsing severe ANCA-associated vasculitis (who had previously received at least 1 dose of cyclophosphamide, methotrexate or azathioprine) and non-inferior in patients with newly diagnosed disease. The ERG also highlighted that longer-term efficacy and safety outcomes of rituximab in treating ANCA-associated vasculitis are unknown, and that there are some potential questions concerning effects on fertility and certain adverse events, especially rates of mortality and malignancies.

5 Comments from other consultees

5.1 The professional groups and clinical specialists confirmed that cyclophosphamide is standard treatment for inducing remission in patients with severe ANCA-associated vasculitis. They advised that methotrexate is an alternative to cyclophosphamide in some situations where there is localised disease, but noted it is associated with a higher risk of relapse. The ongoing MYCYC trial is comparing mycophenolate mofetil, another alternative, with cyclophosphamide.

5.2 The professional groups and clinical specialists advised that rituximab is currently used to induce remission in refractory disease (that is, disease that has remained active despite cyclophosphamide and glucocorticoids). Rituximab is also currently used as to induce remission at time of first relapse. Because of cyclophosphamide's adverse-event profile, rituximab is likely to be used as a first-line remission induction agent in people who cannot tolerate cyclophosphamide, people who wish to preserve their fertility and those with any previous uroepithelial malignancy.

5.3 The professional groups and clinical specialists considered the UK/Europe and USA-based trials with rituximab to be representative of the UK population and practice except that, by including significant renal disease, the trials may have been less representative of the patient group with disease limited to ear, nose and throat. Evidence from the RITUXVAS and RAVE trials suggested that although rituximab was not superior to cyclophosphamide in inducing remission, it was perceived by the professional groups to be associated with fewer severe adverse events. Reported side effects include infusion reactions, which are readily managed. In the short term, adverse reactions such as infection, and neutropenia, are the same for rituximab and cyclophosphamide. Severe lung injury of unknown cause has been reported in a few cases after treatment with rituximab and hepatitis B reactivation has been reported.

5.4 The professional groups and clinical specialists noted that clinical trials have not addressed the potential for long-term harm with rituximab. The long-term safety of repeated courses of rituximab is not known (that is, the cumulative risks of long-term ongoing B-cell depletion on normal immune function). Any side effects directly related to B-cell depletion with rituximab are unlikely to recover in the short term (for example, hypogammaglobulinaemia). Late-onset neutropenia is another potential adverse event that may not be adequately captured in clinical trials.

5.5 The professional groups and clinical specialists indicated that patients with the disease are best treated in secondary or tertiary care specialist clinics. Although rituximab is already used, they noted that funding difficulties may exist and there is variation around the UK, and were aware of the NHS Commissioning draft report on rituximab in ANCA-associated vasculitis (which has subsequently been finalised and published). No additional resources will be required because of the shorter course of treatment for rituximab (2–4 infusions, depending on local protocol), than usually required for cyclophosphamide (7–10 monthly infusions). Rituximab requires fewer concomitant drugs (for example, anti-emetics).

5.6 The submissions from the British Society of Paediatric and Adolescent Rheumatology and British Association for Paediatric Nephrology focused on treating children with ANCA-associated vasculitis. Because the European Medicines Agency's Committee for Medicinal Products for Human Use has issued a positive opinion for rituximab in combination with glucocorticoids to treat severe, active granulomatosis with polyangiitis and microscopic polyangiitis specifically in adults , only the elements of the 2 submissions that are also relevant to the adult population have been summarised here.

5.7 The patient groups and patient expert advised that many patients with vasculitis experience long-term effects of both the disease and its treatment. In addition to the adverse events associated with

cyclophosphamide described earlier, long-term use of prednisolone can cause diabetes, weight gain, cataracts and osteoporosis. Although many patients return to normal or near-normal life, others experience permanent damage such as impaired kidney function (possibly requiring dialysis or transplant), damage to the upper and lower respiratory tract, impaired hearing and loss of balance, loss of vision, and problems associated with neuropathy (for example, loss of mobility and pain). Most patients suffer from severe fatigue. These disabilities may be combined in one individual, leading to poor quality of life and possible inability to work (particularly where there are frequent relapses of the disease). Coping with vasculitis can have a profound effect on mental state, and can strain relationships with partners, family, friends and employers.

5.8 The patient organisation noted that all patients with vasculitis hope for a cure, or at least permanent remission. Some people who have received rituximab suggest that it gives them an immediate psychological lift, and for many it has had a profoundly life-changing effect (see appendix to the Vasculitis UK's submission). The patient perception is that rituximab can help to avoid further organ damage, has fewer side effects than other remission-inducing drugs, is highly effective in both initial induction and treating relapse, and is effective in reducing hospital in-patient stays (which has practical and financial implications for patients who are not well and surviving on welfare benefits), in lowering exposure to cytotoxic cyclophosphamide, reducing steroids dependence and producing longer periods of remission. However, a patient expert noted that some patients react to the infusions, the long infusion time and problems have been reported with white-cell counts and immunoglobulin levels, and that the long-term side effects have not yet been identified.

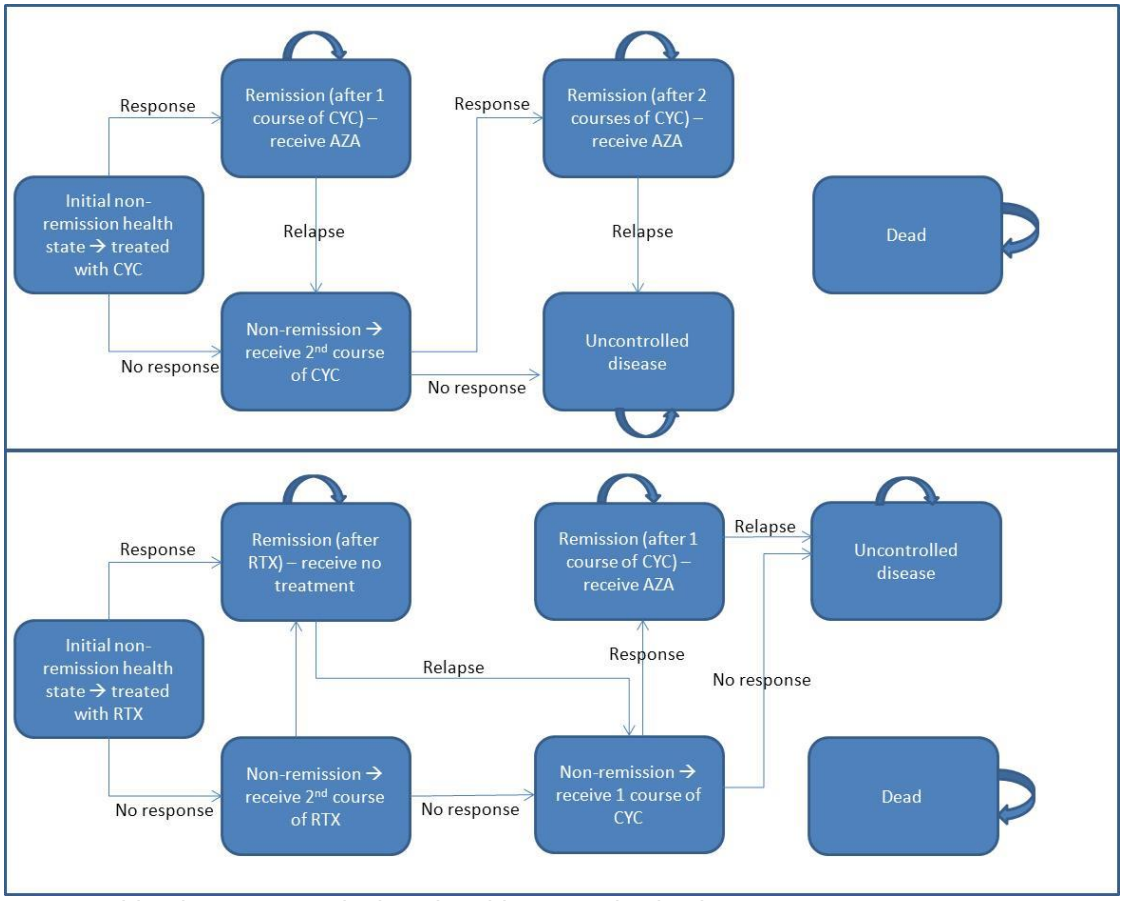
6 Cost-effectiveness evidence

6.1 The manufacturer's systematic review did not identify any studies that reported on the cost effectiveness of treatment for granulomatosis with

polyangiitis and microscopic polyangiitis. The manufacturer therefore submitted a de novo model, which it subsequently updated in its clarification response, that evaluated the cost effectiveness of rituximab compared with cyclophosphamide in patients with ANCA-associated vasculitis. The manufacturer restricted its analysis to inducing remission only and not treating flares or maintenance therapy, in line with its anticipated European marketing authorisation for this indication. The base case included the population from RAVE, and subgroup analyses investigated patients with newly diagnosed disease and with relapsing disease. A separate subgroup analysis estimated the cost effectiveness of rituximab in patients for whom cyclophosphamide was not considered to be the standard of care (because this group was not represented in RAVE). The analysis was conducted from an NHS and personal and social services perspective. A lifetime horizon was used and a 3.5% discount rate was adopted for health benefits and costs.

6.2 The manufacturer developed a Markov model with a similar design to that used in another NICE technology appraisal (NICE technology appraisal guidance 247 'Tocilizumab for the treatment of rheumatoid arthritis [rapid review of technology appraisal guidance 198]). It consists of 4 different health states: non- remission, complete remission, uncontrolled disease and death (see figure 3). 'Complete remission' reflects treatment success as assessed in RAVE, 'non-remission' reflects non-attainment of remission and 'uncontrolled disease' reflects a state of worse health that patients enter after the simulated treatment options have been exhausted.

Figure 3 Structure of manufacturer's economic model



AZA, azathioprine; CYC, cyclophosphamide; RTX, rituximab
Source: page 47 of ERG report

6.3 Patients enter the model in the non-remission health state, receive induction therapy and either transition to the complete remission health state (if they experience remission) or remain in the non-remission health state (if they do not experience remission). During each 6-month cycle, moving from one treatment to the next in each arm's sequence is triggered either by failing to attain complete remission or by the patient eventually relapsing. After receiving all possible treatment options, patients enter after the uncontrolled disease health state. The base-case analysis was designed to compare 2 sequences of treatments:

- In the 'standard of care' sequence, patients receive cyclophosphamide as induction therapy. Patients who experience remission with cyclophosphamide switch to azathioprine during remission. Patients who do not experience remission, or who relapse, receive another

course of cyclophosphamide. Clinical specialist advice to the manufacturer was that a maximum of 2 courses of cyclophosphamide would be used in standard clinical practice. The manufacturer assumed that 72% of patients receive cyclophosphamide intravenously, with the remainder receiving it orally.

- In the intervention sequence, patients receive rituximab as a first-line induction treatment. Patients who experience remission do not receive any further treatment until relapse. Patients who do not experience complete remission receive a further course of rituximab (based on expert opinion because RAVE did not investigate the effects of retreatment). Patients who respond to rituximab are not eligible for retreatment upon relapse because this is outside the scope of the anticipated European marketing authorisation. After relapse following 1 or 2 cycles of rituximab, patients receive 1 course of cyclophosphamide (it was assumed that 72% of patients receive cyclophosphamide intravenously, with the remainder receiving it orally).

After receiving all available induction treatments in the treatment sequence, patients enter the ‘uncontrolled disease’ health state and receive best supportive care.

6.4 The transition probabilities in the manufacturer’s base-case model were based on the primary endpoints from RAVE. A constant rate of relapse was applied in the model and it was assumed that the second course of treatment was associated with a lower probability of achieving remission than the first course. The manufacturer estimated the probability of experiencing remission with the second course of treatment using RAVE results from the subgroup of patients with relapsing disease. The same relative risk was used for retreatment with rituximab and with cyclophosphamide. Transition probabilities for adverse events were also based on RAVE data. Disease-specific mortality risks in the manufacturer’s economic model were derived from a retrospective cohort study of UK patients with ANCA-associated vasculitis.

6.5 The costs used in the manufacturer's economic model comprised treatment-associated costs plus health state costs. Cost data (excluding drug costs) were largely derived from National Reference Costs. Drug costs were derived from British National Formulary Number 64. Average drug costs per cycle were £4689.78 for rituximab, £99.15 for oral cyclophosphamide, £110.84 for intravenous cyclophosphamide, £44.17 for azathioprine, £28.01 for methylprednisone, £1497.96for prednisone, £21.38 for trimethoprim, £25.32 for methotrexate and £459.90 for mycophenolate mofetil. Treatment administration costs per cycle were £721.16 for rituximab and £1802.89 for intravenous cyclophosphamide and it was assumed that these included monitoring costs for rituximab and intravenous cyclophosphamide. Monitoring costs for oral cyclophosphamide and azathioprine were £108. The per-cycle cost of best supportive care for patients with uncontrolled disease was £4415.73. Health state costs were £781.18 for the remission health state and £6312.09 for the non-remission and uncontrolled disease health states.

6.6 The manufacturer's systematic review did not identify any relevant studies that reported usable utility values. Health-related quality of life data were collected in RAVE using the SF-36 questionnaire, which was administered at baseline and at 6 months. The SF-36 scores were converted from the non-remission and remission health states to the EQ-5D in a post-hoc analysis using a published model [Ara and Brazier 2008] and adjusted for age. Disutility adjustments were applied for adverse events.

6.7 The manufacturer's updated base-case results provided at clarification showed that treating ANCA-associated vasculitis using rituximab increased the cost of treatment but was associated with more quality-adjusted life years (QALYs) than cyclophosphamide (table 8).The manufacturer's incremental cost-effectiveness ratio (ICER) for the comparison of rituximab with cyclophosphamide in patients with ANCA-associated vasculitis was £8544 per QALY gained (incremental costs £1391; incremental QALYs 0.1628).

Table 8 Manufacturer's base-case results

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£ per QALY gained)
Rituximab	97,819	11.82	8.19				
Cyclophosphamide	95,819	11.78	8.03	1391	0.0422	0.1628	8544

ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALY, quality-adjusted life year
Source: page 43 of the manufacturer's clarification

6.8 In its response to clarification, the manufacturer provided updated cost-effectiveness results for the comparison of rituximab and cyclophosphamide from its subgroup analyses on patients with newly diagnosed ANCA-associated vasculitis and those with relapsing disease (table 9). Using the base-case number of cyclophosphamide cycles (2 cycles for standard of care and 1 cycle for intervention), the ICERs were £55,175 per QALY gained for the newly diagnosed subgroup and £43,003 per QALY gained for the subgroup with relapsing disease. When it was assumed that all newly diagnosed patients received 2 courses of cyclophosphamide (regardless of treatment-sequence arm), the ICER decreased to £1274 per QALY gained. When it was assumed that patients in the relapsing subgroup would be unable to tolerate additional cyclophosphamide courses, the ICER decreased to £12,556 per QALY gained. Incremental costs and QALYs were not reported for these analyses. The manufacturer advised that the results should be interpreted with a degree of caution because of low patient numbers (approximately 50 in each arm). The manufacturer confirmed that rituximab dominated best supportive care (that is, it cost less but was more effective) in patients who were unable to tolerate cyclophosphamide (incremental costs −£4885; incremental QALYs 0.5386).

Table 9 Manufacturer's subgroup analysis results

Subgroup	Number of cyclophosphamide courses	Manufacturer's rationale	ICER (£ per QALY gained)
Newly diagnosed patients	Standard of care – 2 Intervention – 1	Base-case number of cyclophosphamide cycles	55,175
	Standard of care – 2 Intervention – 2	More plausible number of cyclophosphamide cycles for this subgroup	1274
Relapsing patients	Standard of care – 2 Intervention – 1	Base-case number of cyclophosphamide cycles	43,003
	Standard of care – 0 Intervention – 0	More plausible number of cyclophosphamide cycles for this subgroup	12,556

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Source: page 44 of the manufacturer's clarification response

6.9 The manufacturer performed probabilistic sensitivity analyses to explore uncertainty around the model's key variables in the base case and estimated in its original submission that the probability of rituximab being cost-effective compared with cyclophosphamide in patients with ANCA-associated vasculitis was 57.8% at £20,000 per QALY gained and 64.6% at £30,000 per QALY gained. The manufacturer did not describe the probability of cost effectiveness in its clarification response.

6.10 The manufacturer did one-way deterministic sensitivity analyses to explore the structural uncertainty associated with the model (table 10). The manufacturer reported that its economic model was robust to changes in the main parameters such as health state costs, patient characteristics, the proportion of patients receiving cyclophosphamide intravenously rather than orally, and assuming equal remission rates for rituximab and cyclophosphamide. It indicated that the assumed offset of future costs was a key driver of the model (because of costs in the uncontrolled disease state).

Table 10 Manufacturer's deterministic sensitivity analysis results

Scenario/parameter		Base case	Tested values	ICER (£/QALY)
Cyclophosphamide complete remission rate is equal to rituximab		0.5306	0.6364	24,656
Removal of degradation rate for cyclophosphamide and rituximab		CYC_2 - 0.4200 RTX – 0.4138	CYC_2 -0.5306 RTX_2 -0.6364	12,556
Standardised mortality ratio – set equal in all health states	NR CR UD	4.8 4.32 5.28	4.8	7836
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	9313
Uncontrolled disease utility		0.67	0.75	14,404
			0.58	5800
Intravenous wastage		None	100%	9,954
% of intravenous pulse therapy		72%	33%	12,753
			50%	10,918
			100%	5522
Patient mean weight		67 kg	87 kg	12,618
Number of rituximab infusions		4	2	5570
Frequency of consultant visits (per cycle)			+50%	Rituximab dominates
			-50%	22,176

CYC, cyclophosphamide; NR, no remission; CR, complete remission; RTX, rituximab; UD, uncontrolled disease
Source: page 43 of the manufacturer's clarification response

6.11 The manufacturer presented results for its scenario analysis results (table 11) and noted that the cost-effectiveness estimates were particularly sensitive to changes in treatment sequence because of the small differences in costs and benefits.

Table 11 Manufacturer's scenario analysis results

Parameter/attribute	Base case	Tested values	ICER
Number of cyclophosphamide courses	Standard of care – 2 Intervention – 1	Standard of care – 1 Intervention – 0	£23,634
		Standard of care – 2 Intervention – 0	Rituximab dominated
		Standard of care – 2 Intervention – 2	Rituximab dominates
		Standard of care – 1 Intervention – 1	Rituximab dominates
Which patients are offered a second course of rituximab?	No remission	No patients	£7197
		Relapsing patients only	£9503
		All patients	£9664

Source: page 44 of the manufacturer's clarification response

ERG's critique

6.12 The ERG found that the manufacturer's economic model generally followed NICE's reference case but noted that not all comparators had been included, and that it may have been more appropriate to consider intravenous cyclophosphamide as the primary comparator because of its lower adverse-event risk, and lower cumulative dose potentially allowing additional courses of treatment. The ERG described some uncertainties in the model's population. It considered the manufacturer's decision to focus on severe microscopic polyangiitis and granulomatosis with polyangiitis to be appropriate given that this is the population specified in the anticipated European marketing authorisation and given the populations in RAVE and RITUXVAS. However, the ERG was aware that there is no clear definition of severe disease, and that the definition of severity used in RAVE was closer to that classified as generalised disease in the guidelines. The ERG also noted that RAVE excluded patients with severe renal disease and other life-threatening forms of the disease, meaning that the clinical evidence submitted by the manufacturer did not cover the full population with severe disease. The ERG was also concerned that the manufacturer had used values for weight and body surface area that would be likely to underestimate those of the UK population with ANCA-associated vasculitis.

6.13 The ERG expressed concerns about the treatment sequences used in the manufacturer's economic model:

- The ERG had concerns about the assumption that patients would only receive 2 courses of cyclophosphamide.
- The ERG was unsure why rituximab must only be considered as the first induction treatment received in the manufacturer's economic model. It believed it was relevant to consider the relative cost-effectiveness of rituximab used before and after cyclophosphamide in the treatment pathway. It noted that the NHS Commissioning Board recommended rituximab as first-line treatment in newly diagnosed patients only where avoiding cyclophosphamide is desirable.
- Clinical specialist advice received by the ERG suggested that it would be unlikely that patients who did not respond to an initial course of rituximab would receive a second course (because of a lack of evidence) and they would instead receive an alternative treatment.
- Although it may be clinically reasonable to assume that a patient who previously responded well to rituximab would receive it again upon relapse, there is currently no published evidence to support this.

Based upon clinical specialist advice, the ERG believed that the results presented by the manufacturer should be approached with considerable caution because other more appropriate treatment sequences exist, which have not been modelled by the manufacturer.

6.14 Clinical specialist advice to the ERG suggested that it was very unlikely that patients who experience remission after treatment with rituximab would not receive subsequent maintenance therapy. The ERG noted that it would seem appropriate to assume that patients who experience remission with rituximab then receive maintenance therapy with azathioprine or methotrexate, but that the manufacturer had not included maintenance treatment for patients who experienced remission after receiving rituximab in its economic model.

6.15 The ERG was aware that the manufacturer had not modelled different severities of relapse, despite the availability of data from RAVE for minor and major flares. The ERG's clinical specialists advised that treatment options and the subsequent disease pathway depend critically upon severity of relapse. The ERG noted that the manufacturer had assumed that all relapses lead to immediate retreatment with cyclophosphamide or rituximab because it believed almost all minor relapses would lead to major relapse requiring retreatment. However, the ERG received clinical specialist advice that minor relapses may be controlled in other ways (for example, an increase in corticosteroid dose) and not all patients would progress to a major relapse.

6.16 The ERG had concerns about how the manufacturer had modelled treatment for patients who exhausted treatment with rituximab and cyclophosphamide and progressed to the uncontrolled disease state. The ERG believed it would be more appropriate to have included a health state for non-complete remission (that is, when corticosteroids and other less immunosuppressive treatments are still used). It considered that the failure to model different levels of treatment response and unrealistically high relapse rates may lead to patients in both treatment sequences entering the uncontrolled disease state inappropriately quickly. The ERG stated that ideally the manufacturer's model would have included additional lines of treatment, such as mycophenolate mofetil, leflunomide, azathioprine and methotrexate, because clinical specialist advice received by the ERG suggested that these treatments are likely to be included in the lifetime treatment sequences for patients with generalised, severe ANCA-associated vasculitis. The ERG also believed that these patients would experience disease that was partially controlled through treatment and that the health state would involve a higher utility score than that assumed by the manufacturer for uncontrolled disease. The ERG indicated that costs for this health state would be lower than those assumed by the manufacturer because it was unlikely patients would have

outpatient appointments to receive specialist palliative care every 1.5 weeks.

6.17 The ERG described several concerns about the costs used in the manufacturer's economic model. It stated that health state costs are largest proportion of total costs generated by the manufacturer's economic model (93% for the cyclophosphamide group and 89% for the rituximab group in the manufacturer's base case analysis) and noted the importance of these on the cost-effectiveness results. The ERG noted that certain costs (including some tests and total number of outpatient appointments) were not realistic and believed that these costs were substantially overestimated by the manufacturer, creating a significant bias in favour of rituximab. The ERG also considered that the manufacturer's approach to estimating the drug costs may be biased in favour of the rituximab group (by overestimating the amount of oral cyclophosphamide used in a typical treatment course), and noted that wastage costs had not been included in the manufacturer's base-case analysis.

6.18 For further details of the ERG's critique of the manufacturer's economic analysis, see section 5.3 of the ERG report.

ERG's exploratory analyses

6.19 The ERG corrected several apparent technical errors in the manufacturer's economic model, which included using costs of prednisolone instead of prednisone in line with UK clinical practice. Other cost changes were for cyclophosphamide, trimethoprim and blood tests. The ERG also adjusted the utility value for pneumonia, the relapse rate numbers at risk, distributions for cost parameters, distributions for standardised mortality rates and outpatient appointments, and the mortality risk for patients aged 91 years and older in the uncontrolled disease health state. Cumulatively, these changes decreased the ICER for the comparison of rituximab with cyclophosphamide for all patients with ANCA-associated vasculitis. The ERG's ICER was £6006 per QALY

gained (incremental costs £986; incremental QALYs 0.1642) compared with the manufacturer's base-case ICER of £8544 per QALY gained (incremental costs £1391; incremental QALYs 0.1628). Replacing the cost of prednisone with the cost of prednisolone had the greatest impact.

6.20 In further exploratory analyses, the ERG altered several parameter values in the manufacturer's economic model:

- Body surface area and weight were increased to better reflect patients in RAVE.
- It was assumed that patients who experienced remission after receiving rituximab would receive azathioprine maintenance treatment at the same dosage at patients who experienced remission after cyclophosphamide.
- Relapse rates were re-estimated based on data from patients receiving cyclophosphamide in RAVE who experienced severe flares to reflect the assumption that only severe flares would lead to renewed induction treatment. Given the assumption that patients receiving rituximab induction treatment also received azathioprine maintenance, the same relapse rate was applied to patients in the rituximab group and patients in the cyclophosphamide group.
- Costs and utility values in the uncontrolled disease state were amended to reflect that patients in this state are likely to have some disease control.
- The number and costs of routine tests were amended to reflect recommendations in published guidelines.
- Methylprednisolone administration costs were increased.
- Costs of X-rays and computerised tomography scans were taken from NHS reference costs.
- Wastage costs were included.
- Number of outpatient appointments was reduced.

Upon adding these changes in the manufacturer's economic model to those described in section 6.18, the ERG's cumulative ICER further increased to £26,347 per QALY gained (incremental costs £5704; incremental QALYs 0.2165) for the comparison of rituximab with cyclophosphamide for the full population of patients with ANCA-associated vasculitis.

6.21 The ERG modelled several treatment sequences that it considered to be more appropriate than those in the manufacturer's submission, and these are described in sections 6.21–6.25. The ERG investigated how different treatment sequences could impact on the cost-effectiveness estimates for the full patient population with ANCA-associated vasculitis in the manufacturer's economic model (table 12). Adding rituximab to the treatment sequence after 2 courses of cyclophosphamide gave an ICER of £12,075 per QALY gained (incremental costs £3894; incremental QALYs 0.32). Using rituximab after 1 course of cyclophosphamide increased the ICER to £69,710 per QALY gained (incremental costs £355; incremental QALYs 0.0051) compared with using it after 2 courses. Using rituximab as first-line treatment further increased the ICER to £127,456 per QALY gained (incremental costs £579; incremental QALYs 0.0045) compared with using rituximab second line. At £30,000 per QALY gained, the probability of rituximab being cost effective after 2 courses of cyclophosphamide was 58.3%. The probability of excluding rituximab from the treatment sequence being cost effective was 11.7%.

Table 12 ERG's exploratory analyses: alternative treatment sequences for the full population

Treatment sequence	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
CYC → CYC → BSC	18,927	8.5810	–	–	–
CYC → CYC → RTX → BSC	22,821	8.9035	0.32	3894	12,075
CYC → RTX → CYC → BSC	23,176	8.9086	0.0051	355	69,710
RTX → CYC → CYC → BSC	23,755	8.9131	0.0045	579	127,456

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 108 of the ERG's report

6.22 The ERG did exploratory analyses for the population with newly diagnosed ANCA-associated vasculitis (table 13). Adding rituximab to the treatment sequence after 2 courses of cyclophosphamide gave an ICER of £12,851 per QALY gained (incremental costs £3783; incremental QALYs 0.29). Using rituximab after 1 course of cyclophosphamide increased the ICER to £81,604 per QALY gained (incremental costs £364; incremental QALYs 0.0045) compared with using rituximab after 2 courses of cyclophosphamide. The ICER for using rituximab as a first-line treatment further increased the ICER to £317,038 per QALY gained (incremental costs £843; incremental QALYs 0.0027) compared with using rituximab second line. At £30,000 per QALY gained, the probability that using rituximab after 2 courses of cyclophosphamide was cost effective in patients with newly diagnosed disease was 59.7%. The probability of excluding rituximab from the treatment sequence being cost effective was 13.9%.

Table 13 ERG's exploratory subgroup analyses: alternative treatment sequences for the newly diagnosed population

Treatment sequence	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
CYC → CYC → BSC	18,646	8.6491	–	–	–
CYC → CYC → RTX → BSC	22,429	8.9435	0.29	3783	12,851
CYC → RTX → CYC → BSC	22,794	8.9480	0.0045	364	81,604
RTX → CYC → CYC → BSC	23,637	8.9507	0.0027	843	317,038

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 110 of the ERG's report

6.23 The ERG did exploratory analyses on the population of patients with recurrent ANCA-associated vasculitis who were eligible for further treatment with cyclophosphamide (table 14). Adding rituximab to the treatment sequence after cyclophosphamide gave an ICER of £11,129 per QALY gained (incremental costs £4702; incremental QALYs 0.4225). The ICER for rituximab as first-line treatment was £51,842 per QALY gained (incremental costs £325; incremental QALYs 0.0063) compared

with second-line treatment. The probability of rituximab being cost effective after 1 course of cyclophosphamide was 51.3% at £30,000 per QALY gained. The probability of excluding rituximab from the treatment sequence being cost effective is 10.4%.

Table 14 ERG's exploratory subgroup analyses: alternative treatment sequences for patients with recurrent disease and eligible for additional cyclophosphamide

Treatment sequence	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
CYC → BSC	17,593	8.2548	–	–	–
CYC → RTX → BSC	22,296	8.6773	0.4225	4702	11,129
RTX → CYC → BSC	22,621	8.6836	0.0063	325	51,842

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 112 of the ERG's report

6.24 The ERG did exploratory analyses on the population of patients with recurrent ANCA-associated vasculitis who were ineligible for further cyclophosphamide treatment (table 15). Using rituximab instead of best supportive care gave an ICER of £10,699 per QALY gained (incremental costs £5385; incremental QALYs 0.5033). The ERG assumed that patients who could not tolerate further cyclophosphamide treatment and were receiving best supportive care moved directly to a low-grade disease health state (with partial disease control), and explained that this assumption limited the analysis because active comparators were excluded. At £30,000 per QALY gained, the probability of rituximab being cost effective was 90.4%. The probability of excluding rituximab from the treatment sequence being cost effective was 9.6%.

Table 15 ERG's exploratory subgroup analyses: alternative treatment sequence for patients with recurrent disease and ineligible for additional cyclophosphamide

Treatment sequence	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
BSC	15,747	7.9379	–	–	–
RTX → BSC	21,132	8.4412	0.5033	5385	10,699

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 114 of the ERG's report

6.25 The ERG did an exploratory subgroup analysis on patients who were unable to tolerate cyclophosphamide (table 16). This subgroup did not necessarily have recurrent disease, but could not take cyclophosphamide for a reason other than exceeding the maximum recommended lifetime cumulative dose. Model parameter inputs were based on the full patient population in RAVE. Using rituximab instead of best supportive care gave an ICER of £11,277 per QALY gained (incremental costs £5437; incremental QALYs 0.48). The ERG assumed that patients who could not tolerate further cyclophosphamide treatment and were receiving best supportive care moved directly to a low-grade disease health state (with partial disease control), and explained that this assumption limited the analysis because active comparators were excluded. At £30,000 per QALY gained, the probability of rituximab being cost effective in patients who cannot tolerate cyclophosphamide was 90.5%. The probability of excluding rituximab from the treatment sequence being cost effective was 9.5%.

Table 16 ERG's exploratory subgroup analyses: alternative treatment sequence for patients who are intolerant to cyclophosphamide

Treatment sequence	Total costs	Total QALYs	Incremental QALYs	Incremental costs	ICER (£ per QALY gained)
BSC	15,747	7.9379	–	–	–
RTX → BSC	21,184	8.4200	0.48	5437	11,277

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 116 of the ERG's report

6.26 After receiving feedback from clinical specialists on its exploratory analyses, the ERG did other scenario analyses on the full patient population to further explore uncertainty associated with some parameters used in the economic model (table 17). The parameters tested were: reduced administration costs for methylprednisone and cyclophosphamide (because of shorter infusion time); substituting co-trimoxazole for trimethoprim; fewer cyclophosphamide infusions (6 instead of 10); and increased weight and body surface (to reflect the UK population with ANCA-associated vasculitis). These amendments had little cumulative

impact on ICER for adding rituximab to the treatment sequence after 2 courses of cyclophosphamide treatment, which increased slightly from £12,075 per QALY gained (ERG's base-case ICER) to £12,670 per QALY gained. However, the cumulative ICERs for using rituximab earlier in the treatment sequence increased more markedly because of reduced costs for intravenous cyclophosphamide and increased costs for rituximab (owing to higher body surface area). The ICER for using rituximab after 1 course of cyclophosphamide was £117,545 per QALY gained compared with after 2 courses of cyclophosphamide, and the ICER for using rituximab as first-line treatment was £191,013 per QALY gained compared with using it as second-line treatment. The ERG anticipated that these findings using the full patient population would be mirrored in the subgroups of patients who were newly diagnosed or had recurrent disease.

Table 17 ERG's additional exploratory scenario analyses (full population)

Treatment sequence	ERG's base-case ICER (£/QALY gained)	Cumulative ICER for additional scenario analyses (£/QALY gained)
CYC → CYC → BSC	–	–
CYC → CYC → RTX → BSC	12,075	12,670
CYC → RTX → CYC → BSC	69,710	117,545
RTX → CYC → CYC → BSC	127,456	191,013

BSC, best supportive care; CYC, cyclophosphamide; RTX, rituximab
Source: page 120 of the ERG's report

7 Equality issues

7.1 During the draft scope consultation and in consultee submissions, it was suggested that children should be included in the population. However, the anticipated wording of the European marketing authorisation specifies treatment for adults so this does not represent a potential equality issue that would need to be addressed by the Committee because rituximab will only be appraised within its licensed indication.

7.2 During the scoping process, it was noted that there might be an increase in vasculitis in first- or second-generation immigrant populations.

Consultees also stated that because this treatment is administered intravenously, there might be difficulties in accessing treatment for patients with transport concerns (such as those living in rural areas, with financial issues, or with physical disabilities). These issues fall outside the remit of a NICE technology appraisal, and it is not expected that an appraisal will impose any restrictions in terms of the locality of patients or otherwise limit access for people with a disability.

8 Innovation

8.1 The manufacturer explained that rituximab is the first monoclonal antibody to be approved for treating vasculitis, which may encourage additional medicines to be studied and provide a step change in managing the condition. The manufacturer's submission stated that it is known that cyclophosphamide reduces the fertility in both males and females but current alternative induction agents are considered less effective, whereas rituximab is not inferior to cyclophosphamide and maintains patients' fertility. The manufacturer stated that the benefit to patients of maintaining fertility while treating the disease effectively cannot currently be captured in the QALY.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

There is no related guidance for this technology.

Appendix B: Clinical efficacy section of the draft European public assessment report

2.5.3. Discussion on clinical efficacy

[redacted]

[redacted]

[redacted]

[redacted]

2.5.4. Conclusions on the clinical efficacy

[redacted]