CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Tocilizumab for treating giant cell arteritis
Erratum Document

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1 Summary

Giant Cell Arteritis (GCA) is an inflammatory vasculopathy affecting large and medium-sized arteries. The company submission (CS) stated that GCA is a potentially life-threatening condition linked with substantial impairment of the day-to-day functioning of patients. The ERG believes that describing GCA as a potentially life-threatening condition is not well substantiated: whilst GCA may rarely lead to life threatening events such as aortic aneurysm rupture or stroke, at a population level there is no clear evidence that long-term mortality is significantly increased in patients with GCA compared to individuals without GCA. The CS describes two clinical subtypes of GCA: cranial GCA which is the most typical presentation; and large vessel (LV) GCA which is less common. Cranial GCA can result in ischaemic manifestations such as severe headache, jaw claudication and visual impairment. Clinical advice to the ERG indicated that once treatment is initiated it is rare for patients to develop vision loss. The CS describes the complications of LV GCA as aortic aneurysms, aortic dissection and coronary arteritis.

GCA is a rare condition, it is estimated that around 1 in every 4,500 people will develop it in the UK each year. The CS stated that GCA primarily affects adults ≥50 years old. The risk increases with age, with the highest rates being observed between 70 and 80 years. The CS correctly stated that there are no NICE guidelines for GCA; however, the British Society for Rheumatology (BSR) has developed clinical practice guidelines to advise the diagnosis and management of GCA. The intervention presented is tocilizumab (TCZ), which received marketing authorisation on 21st September 2017.

The CS reports that current treatment mainly consists of high dose GC (usually prednisone – the ERG notes that in the UK this is usually prednisolone) followed by long-term steroid tapering. Complicated GCA (evolving vision loss or established vision loss) is treated with an initial dose of 60 mg or above, whereas uncomplicated GCA (no jaw or tongue claudication or visual symptoms) is treated with 40-60 mg. Once signs and symptoms of GCA are absent patients are slowly tapered off GC.

1.1 Critique of the decision problem in the company's submission

The population for this submission were adults with GCA, which was in line with the NICE scope definition. The ERG clinical advisor stated that the GiACTA trial population was generally applicable to patients seen in NHS practice, with the exception that there were a higher proportion of patients with large vessel GCA, than is typically seen in NHS practice.

The intervention presented in the CS was tocilizumab, which matched that specified in the NICE scope. The recommended posology is 162 mg of subcutaneous tocilizumab once every week in combination with a tapering course of GC. In the GiACTA trial there were two tocilizumab arms: once a week (QW) dosing and one every other week (Q2W) dosing; only the once a week dosing is

The GiACTA trial investigated the clinical effectiveness of tocilizumab in 251 adults over 50 years old (mean age 69 years) with new-onset or relapsing giant cell arteritis. The trial consisted of four arms, however this report focuses on the arms most applicable to UK clinical practice: 162mg of tocilizumab once a week with a 26 week GC taper (TCZ QW+26) (n=100) and placebo with a 52-week GC taper (PBO+52) (n=51). The tocilizumab treatment duration was 52 weeks.

Sustained remission

Tocilizumab was more effective than placebo in sustaining remission, with a significantly higher number of participants with sustained remission at Week 52 in the TCZ QW+26 arm (56.0%) compared with the PBO+52 arm (17.6%); the difference in percentage of responders was 38.35 (99% CI 17.89 to 58.81) ($p<0.0001$).

The GiACTA trial has an ongoing Part 2, which is an open-label extension including patients from Part 1 who will be followed for an additional 2 years. Preliminary results from Part 2 were that 33% of TCZ QW+26 responders flared after discontinuation of tocilizumab, indicating that for a sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients. Therefore, further reliable and accurate research is needed to determine the long term effectiveness of tocilizumab in maintaining remission in patients with GCA.

Flare

The hazard ratio (0.37, 99% CI: 0.2-0.7) showed a statistically significant lower risk of flare in patients in the tocilizumab group compared to the placebo+52 week group ($p<0.0001$). The mean annualised relapse rate for multiple flares observed in each patient was 1.30/year in the PBO+52 arm (median: 1) compared with 0.41/year in the TCZ QW+26 arm (median:0).

Cumulative dose of GC

There was a statistically significant lower median cumulative GC dose to Week 52 in the TCZ QW+26 group (1862mg) when compared with the PBO+52 group (3817.5mg) ($p<0.0001$).

Sub-group analyses

Sub-group analyses by disease status at baseline (new-onset or relapsing) for Sustained Remission at week 52, for Time to GCA flare, and for cumulative GC dose were reported in the CS.

The difference in the proportion of patients achieving sustained remission at Week 52 between the TCZ QW+26 group and the PBO+52 group was similar among new-onset (37.9%) and relapsing GCA patients (38.5%). However, the proportion of patients in sustained remission in the PBO+52 group was lower for relapsing patients (14.3%) than for new-onset patients (21.7%).

sustained remission at Week 52 and the secondary outcome of time to first GCA flare may be biased due to not all patients being in remission at baseline. The chance of a placebo patient, who was not in remission at baseline, achieving remission at week 12 may be biased against by the imposition of the GC taper from baseline. In contrast, the time of first GCA flare may be biased in favour of placebo due to not all patients being in remission at baseline.

The generalisability of the GiACTA trial to the UK GCA population is generally appropriate, however there are some differences:

- The number of patients from the UK in the TCZ QW+26 arm of the trial was only 7.

- The GiACTA trial includes both new-onset and relapsing GCA patients. Clinical advice to the ERG indicated that these two subgroups of patients would be treated differently in practice. The analysis of the GIACTA trial can be criticised because it did not take into account the difference between new-onset and relapsing patients, nor that between those who were in remission at baseline and those who were not. Randomisation was stratified by baseline prednisone dose only. Whilst there was a significant difference in baseline prednisone dose between new-onset and relapsing patients, this stratification will not account for the other differences between the new-onset and relapsing populations. Sub-group analyses by disease status at baseline (new-onset or relapsing) for sustained remission at week 52, for time to GCA flare, and cumulative GC dose were reported in the CS.

- The baseline characteristics of the GiACTA population appear to be fairly representative of the UK GCA population. However, the ERG notes that there is a difference in the mean age of patients in the GiACTA trial (69.05 years) and that from the UK CPRD data source (73 years). Also, overall there was a higher ratio of large vessel GCA patients to cranial GCA patients than would be seen in NHS practice. However, this may be due to the difference in diagnostic techniques such as vascular imaging, which is more effective in diagnosing large vessel GCA patients. Therefore, the rates of LV GCA in the UK may be under estimated.

- The trial uses a 26 week GC taper for three of the four treatment groups. The tapering regimen recommended by BSR adds up to a minimum of 52 weeks. Hence, the placebo arm with a 52 week GC taper is most relevant to UK clinical practice. The 26 week taper used with tocilizumab is likely to be attempted in clinical practice, with the aim of reducing the GC load.

- Although the trial included four treatment arms the only comparison relevant to NHS practice is that between TCZ+26 and PBO+52

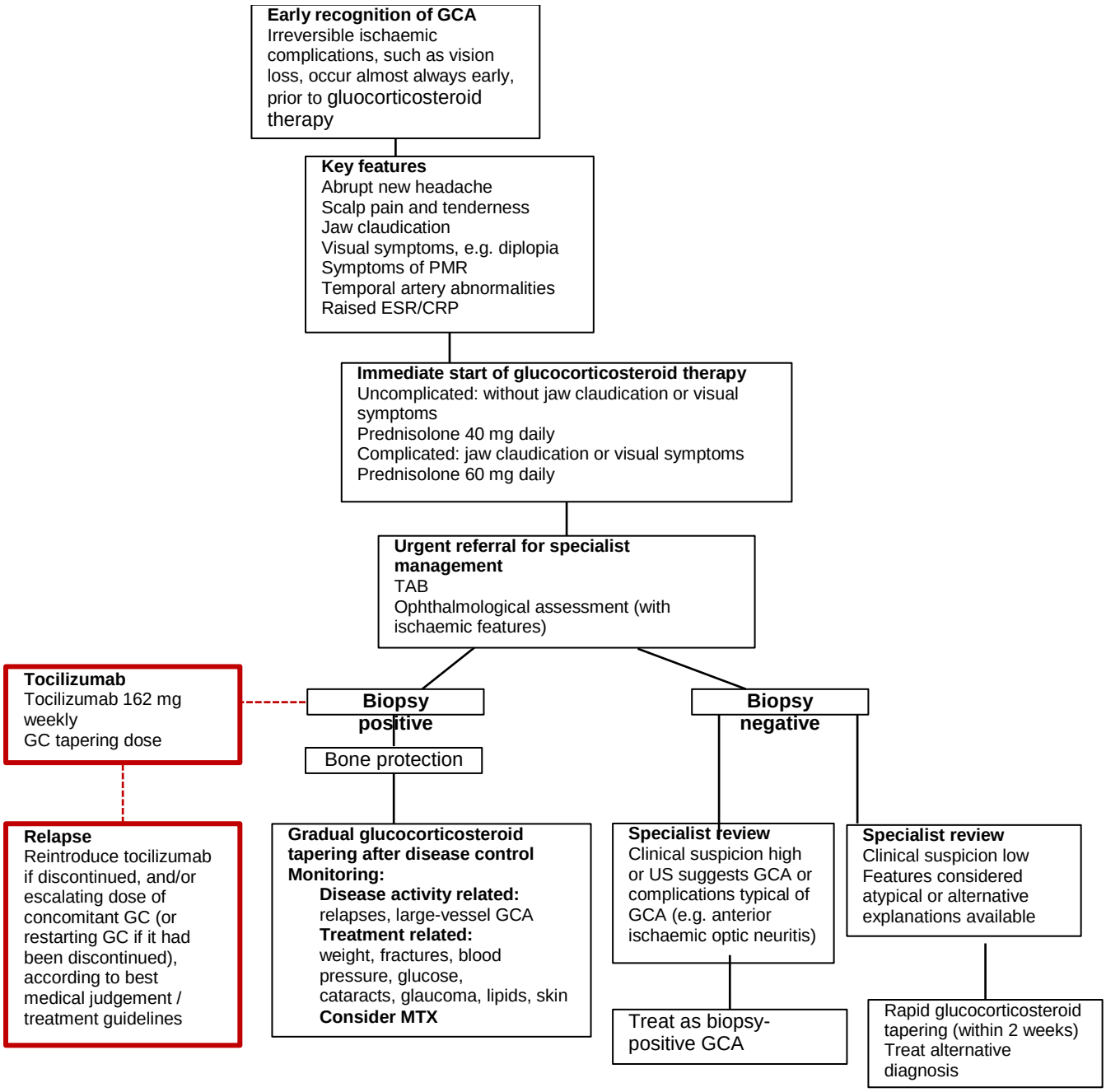
1.4 Summary of cost effectiveness submitted evidence by the company

of 52 weeks and a cumulative GC dose between 3.6g and 7.4g over approximately 1 - 1.5 years, in those patients who do not experience a relapse or flare.[16] However, if a patient relapses or flares the GC dose needs to be increased and then tapered accordingly, which can increase the duration of treatment and the cumulative GC dose substantially. The CS states that at least 50% of GCA patients are reported to relapse during GC tapering[17, 18] but also states that the majority of relapses are associated with rapid tapering.[15] However, the ERG notes that patients with GCA rarely relapse while receiving more than 20mg of daily GC; the majority of relapses occur when patients GC dose is tapered to below 10mg/day.[19] Patients receiving a high cumulative dose of GC often experience GC-related adverse effects (AEs) due to the toxicity associated with long term steroid use. The CS stated that approximately 86% of GCA patients experience GC-related AEs after 10 years of follow up.[17] These patients are at an increased risk of developing diabetes, osteoporosis, fractures and serious infections compared to patients receiving a lower dose of GC.[18]

Other immunosuppressive drugs have been investigated and considered as alternatives to GC or as GC sparing drugs; however none have been shown to be effective at inducing and maintaining remission once GC treatment has been discontinued.[20-23] Methotrexate which is an immunosuppressant used in clinical practice has limited and insufficient evidence to support its use in place of GC treatment.[24, 25] Clinical advice to the ERG confirmed that methotrexate is used in clinical practice but only alongside GC treatment, and only because the options for steroid sparing are so limited: there is no good evidence to support the use of methotrexate and it is often poorly tolerated in patients with GCA.

The company's overview of current service provision is generally appropriate and relevant to the decision problem; however, the BSR guideline for the treatment pathway was slightly unclear. The typical treatment pathway for GCA patients, with the anticipated place of tocilizumab within the pathway, is presented in Figure 1 but suggests that urgent referral for specialist management only happens if urgent GC therapy doesn't work. However, all patients suspected to have GCA receive urgent GC treatment which usually controls the symptoms. The patient's GC treatment is then tapered. Unfortunately, tapering GC can lead to relapse and return of symptoms, and continued treatment with GC is associated with GC side effects and GC dependence. Therefore, the CS states correctly that an effective non-GC therapy that was steroid sparing would be valuable in the treatment of GCA. The CS is proposing that tocilizumab along with a GC tapering dose is introduced after initial treatment with GC. The CS suggests that tocilizumab would reduce the cumulative GC dose received by patients and therefore reduce the GC-related AEs. This may be achieved by lowering the relapse rate and increasing the remission period but also by having a shorter GC tapering regimen alongside tocilizumab.

Figure 1 Pathway for management of GCA (CS Figure 1 Page 24)



3 Critique of company's definition of decision problem

3.1 Population

The CS described the relevant population as "Adults with Giant Cell Arteritis" This population matched that specified in the NICE scope.

The clinical effectiveness evidence presented is primarily from patients with GCA from the GiACTA randomised controlled trial (RCT). The trial population included adults over 50 years old who had either new-onset GCA or relapsing GCA and only included patients with active GCA disease within 6 weeks of baseline visit. The ERG clinical advisor stated that the GiACTA trial population is generally applicable to patients seen in NHS practice, with the possible exception of the proportion of patients with large vessel GCA. This is because around 40% of patients in GiACTA were eligible primarily on the basis of large-vessel imaging whereas, in the UK around 95% of patients with GCA present with cranial features and relatively few are diagnosed on the basis of large-vessel imaging. However, this difference may relate in part to differences in the availability of vascular imaging in the UK versus countries where services operate on a fee-for-service model. Furthermore, the ERG noted that the mean age of patients in the GiACTA trial was 69 years old, which is lower than the mean age of GCA patients in the UK CPRD data source (73 years). Therefore, the population in the GiACTA trial is not wholly representative of the UK GCA population.

The CS also included one phase II, randomised, double-blind, placebo-controlled trial as supporting evidence. Study NCT01450137 included thirty adult patients with new-onset or relapsing GCA who were randomised to receive GCs and either tocilizumab (20 patients) or placebo (10 patients).

3.2 Intervention

The intervention presented in the CS was tocilizumab, which matches that specified in the NICE scope. The recommended posology is 162 mg of subcutaneous tocilizumab once every week in combination with a tapering course of GC. Tocilizumab can be used alone following discontinuation of GC but is not used as monotherapy for the treatment of acute relapses.

Tocilizumab received marketing authorisation, on 21st September 2017. The Committee for Medicinal Products for Human Use (CHMP) Positive Opinion was granted on 20 July 2017 for subcutaneous tocilizumab for the "treatment of GCA in adult patients". The FDA approved tocilizumab subcutaneous injection for the treatment of GCA on 23 May 2017.[26, 27]

The GiACTA trial uses the 162 mg subcutaneous dose of tocilizumab as per the licence. In the trial there were two tocilizumab arms: once a week (QW) dosing and once every other week (Q2W) dosing; only the once a week dosing is licensed and therefore, this report will present tocilizumab

- The GiACTA trial includes both new-onset and relapsing GCA patients. Clinical advice to the ERG indicated that these two subgroups of patients would be treated differently in practice. New-onset GCA patients are typically easier to treat and can often control their disease using GC treatment within one year. Clinical advice suggested that tocilizumab would preferably be used in relapsing patients and new-onset patients who are at high risk of mental health problems, or pre-existing diabetes or osteoporosis /fragility fracture, or those who experience adverse effects from GC. Therefore, the GiACTA trial population may not be wholly generalizable to the population treated in clinical practice.
- The baseline characteristics of the GiACTA population appear to be fairly representative of the UK GCA population. However, the ERG notes that there is an important difference in the mean age of patients in the GiACTA trial (69.05 years) and that from the UK CPRD data source (73 years). The ERG considered that the age reported in the UK CPRD data source more appropriately reflects the relevant population in England and Wales. Also, overall there were a higher proportion of large vessel GCA patients than cranial GCA patients. Clinical advice to the ERG indicated that, in practice, there would typically be more cranial GCA patients.. However, this may be due to the difference in international diagnostic techniques such as vascular imaging, which is more effective in diagnosing large vessel GCA patients. Therefore, the rates of LV GCA in the UK may be under estimated.

- The trial uses a 26 week GC taper for three of the four treatment groups. This is much shorter than that used in UK clinical practice. Clinical advice to the ERG indicated that, in practice, the average length of GC treatment is just over 2 years. Furthermore, the tapering regimen recommended by BSR adds up to a minimum of 52 weeks.[15] Importantly, several studies have shown that both the initial GC dose and the tapering schedule appear to influence the relapse rate. Higher relapse rates have been reported in the context of clinical trials with adjuvant therapies where GC tapering is more aggressive than in routine clinical practice.[13] Consequently, although the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, uncertainty remains concerning the generalisability of this tapering regimen and the associated relapse rate to a longer GC tapering regimen (18-24 months) more conventionally achieved. In summary, the placebo arm with a 52 week GC taper is most relevant to UK clinical practice.

3.2.1 Summary of results of GiACTA

Disease Remission

The primary endpoint of sustained remission at Week 52 of both tocilizumab groups compared with patients receiving placebo + 26 week GC taper was reported on pages 38-39 of the CS. However, the

these groups experiencing a flare. In relapsing patients it was 165 days in the PBO+26 group and 274 days in the PBO+52 group but was not calculable in the tocilizumab treatment groups. The CS did not report the hazard ratios for these subgroups and so the ERG performed the analysis. The median time to GCA disease flare in new-onset GCA patients was 169 days in the PBO+26 group and was not calculable for the other three groups due to fewer than 50% of the new-onset patients in these groups experiencing a flare. In relapsing patients it was 165 days in the PBO+26 group and 274 days in the PBO+52 group but was not calculable in the tocilizumab treatment groups. The ERG analysed both subgroups and found that the relative treatment effect was slightly less in the new-onset patients (HR 0.44, 95% CI 0.14 -1.32; (p=0.004)) compared with the relapsing patients (HR 0.36, 95% CI 0.13 – 1.00; (p=0.04)

Cumulative GC dose by disease status at baseline (new-onset or relapsing)

Cumulative GC dose by disease status at baseline (new-onset or relapsing) is presented in the CS Section E1.4. The NHS relevant arms are given in Table 5 below.

Table 1 Cumulative GC dose by disease status at baseline (new-onset or relapsing) (adapted from CS Appendix E 1.4 Table 11)

	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100
New-onset		
n	23	47
Mean (SD)	4136.83 (2055.62)	2406.67 (1341.88)
Median	3817.50	1942.00
Range	2017.5–10275.0	630.0–6602.5
95% CI of the Median	2577.5, 4584.5	1822.0, 2519.0
Relapsing		
n	28	53
Mean (SD)	4250.06 (2504.68)	1823.96 (1100.85)
Median	3785.50	1385.00
Range	822.5–10697.5	658.0–5912.0
95% CI of the Median	2222.5, 5372.5	1127.0, 1862.0

The mean differences between cumulative dose in the TCZ QW arm and the PBO+52 arm for these subgroups were not compared formally, but it was numerically higher in the relapsing patients (2426 mg compared with 1730 mg) despite their lower GC dose at baseline (Table 3).

Resource utilisation and costs	The treatments costs of tocilizumab and GC treatment included the acquisition, administration and monitoring costs. Separate heath state costs were applied based on remission status and associated use of steroids (on/off steroids and on maintenance steroids) and flare episodes. Additional costs were also assigned to GCA related complications and GC related AEs.	The treatment costs of tocilizumab and GC were based on published prices. A separate analysis was reported based on the approved PAS for tocilizumab. The cost of conventional GC treatment was based on published prices for prednisone. Health state costs were based on third-party market research undertaken by the company. The costs of GCA related complications and GC related AEs were derived from the external literature.	
Discount rates	3.5% for costs and outcomes	NICE reference case	Section B.3.2.2; p95
Population and Subgroups	The model only considers the overall ITT population.	The overall ITT population was justified as being the most relevant to the decision problem based on the marketing authorisation and NICE scope. Results were not presented for each of the 2 patient subgroups identified within the NICE scope (newly diagnosed and relapsed/refractory). This was justified based on the favourable cost-effectiveness results for the overall population, the lack of difference in efficacy reported between the subgroups and the lack of statistical power. Separate results for these subgroups were subsequently provided and included in the company response to the points for clarification.	Section B.3.9; p141-142
Sensitivity analysis	Univariate and probabilistic sensitivity analysis and scenarios.	NICE reference case	Section B3.8; p131-141
Key: GCA: Giant Cell Arteritis; ITT: Intention To Treat; GC: Glucocorticoids; AE: Adverse Events; NICE: National Institute for Health and Care Excellence			

3.2.2 Model structure

The submission is based on a semi-Markov model using a weekly cycle length. The conceptualisation of the model is stated to have been informed by the disease aetiology, trial data, NICE Scientific Advice and expert opinion (clinician and HTA).

The model structure is shown in Figure 6 and includes seven separate health states:

- On remission and on steroid;
- On remission and off steroid;
- On relapse/flare;
- On remission and on maintenance steroids (escape);
- GCA-related complications;
- Steroid-related AEs;
- Death.

The submission states that people with GCA enter the model either on relapse/flare or in the remission state and treatment is then initiated with TCZ QW plus prednisone or prednisone alone. After achieving remission, patients then follow the GiACTA protocol for steroid tapering (26 weeks for TCZ QW and 52 weeks for prednisone alone) and remain in remission until their first flare.

Transitions from the initial remission state are estimated via time-dependent transition probabilities. These probabilities are estimated using parametric survival analysis based on the Kaplan-Meier data from the GiACTA trial on time to first flare. The use of parametric survival analysis allows the probability of an initial flare to be time-dependent and provides a basis for extrapolation beyond the 52-week follow-up of the GiACTA trial.

Following a first flare, patients then transition to a separate remission state – 'On remission and maintenance steroids (escape)'. The separate remission state is used to distinguish the initial remission period from subsequent remission periods. This separation permits different transition probabilities to be assigned within these periods. The probability of further relapse/flare events following a subsequent remission was estimated using a separate Poisson regression based on data from the subgroup of patients following an initial flare from the GiACTA trial. A key assumption of the model is that the probability of a relapse/flare during each subsequent remission is higher than the probability during the initial remission period and is constant with time.

The separate remission and relapse/flare states are used to characterise the natural history of GCA. Separate transition probabilities for TCZ-QW+26 and PBO+52 are used to quantify the impact of the alternative treatments in terms of GCA symptom control (i.e. duration of initial and subsequent remission and number of relapse/flare episodes). Additional states are also incorporated to capture GCA-related complications (visual loss and stroke) and the potential steroid sparing effect of tocilizumab in terms of reducing GC-related AEs (fracture and diabetes).

Estimates of the distutility of GCA related complications (vision loss, minor and major stroke) were derived from a study by Luqmani et al. 2016. The valuation approach used to estimate these distutilities was not stated in the submission. Cross-checking with the source reference suggests that the disutility of visual loss were based on values estimated using a time trade-off approach. The valuation approach was not stated for stroke complications. The ERG identified minor discrepancies between several of the estimates reported in the company model and those reported in Luqmani et al. The reason for these discrepancies was unclear but the magnitude was sufficiently small that these differences were not considered likely to have any material impact on the ICER results.

3.2.3 Resources and costs

The CS provided a detailed description of resource use and costs. These related to: drug acquisition, monitoring, concomitant medication and costs related to the health states and GCA-related complications and GCA-related AEs.

The acquisition and monitoring costs of treating GCA patients with either TCZ-QW or prednisone alone are summarised in Table 15.

Table 2: Acquisition, administration and monitoring cost assumptions

Items	Intervention: Tocilizumab subcutaneous formulation	Comparator: Prednisone
Technology cost	£913.12 for 4 pre-filled syringes with 162 mg (PAS [redacted])	£26.70 for 30 tablets at 5 mg each (Following clarification, the company altered the cost data to use the lower cost of prednisolone: £0.81 for 28 tablets at 5 mg each)
Cost of treatment	The annual cost of tocilizumab treatment for a GCA patient on the weekly dosing regimen (QW) would be £11,870.56 based on list prices (PAS cost equivalent [redacted] Concomitant GC treatment for the first year is modelled to be £687.06, with an additional £88.01 needed for treating flare.	The actual cost of GC treatment varies greatly for people with GCA, depending on relapse/flare or remission: a patient on maintenance treatment may have a dose as low as 5 mg/day, with the BSR Guidelines recommending up to 60 mg prednisone daily for acute relapse/flare treatment. The first year GC costs modelled for GCA patients were £885.62, with an additional £235.79 needed for treating flare.
Administration cost	Self-injection: no administration costs	Oral: no administration costs
Monitoring cost	£3 per blood test, one blood test performed every 6 weeks while on tocilizumab	Monitoring costs are associated with high-dose daily GC treatment while in relapse/flare
Tests	Not relevant	Not relevant

Replicated from company submission

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section focuses on the additional analyses undertaken by the ERG to explore the key areas of uncertainty and concern highlighted in Section 5.

These analyses are undertaken using the revised model submitted by the company following the points for clarification. As stated in the previous section, the revised model included corrections to programming, alternative costing assumptions for GC treatment and the ability to assess the ITT populations as well as the newly diagnosed and relapsed/refractory subgroups.

6.2 ERG corrections and adjustments to the company's base case model

The ERG could not replicate or validate the company's probabilistic results for their base-case analysis for the ITT population. Also, the estimates provided by the company for the separate subgroups were incorrect and reported to be the same as the ITT population. Additional simulations (1,000 iterations) were undertaken by the ERG and revised ICERs estimated by dividing the mean incremental cost by the mean incremental QALYs across the PSA.

The probabilistic results are reported in Table 30, Table 31 and Table 32 for the ITT population, newly diagnosed and relapsed/refractory subgroups.

The ERG revised probabilistic ICERs are: £26,914 (ITT population); £35,766 (new-onset) and £21,000 (relapsed-refractory). The probability that tocilizumab treatment is cost-effective at a threshold value of £30,000 per additional QALY is 0.61 (ITT population), 0.40 (new-onset subgroup) and 0.73. (relapse/refractory subgroup) compared with GC treatment alone.

Table 3: ERG revised base-case probabilistic ICER results - ITT population

	Total estimates				Incremental estimates				
Technologies	**Total Flares**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incr. Flares**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER (£/QALY)**
Prednisone alone	20.24	[redacted]	12.42	8.44	-12.29	£12,081	0.02	0.45	£26,914
Tocilizumab with prednisone	7.95	[redacted]	12.44	8.89					