NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tocilizumab for treating giant cell arteritis [1051]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche
   - British Society of Rheumatology – endorsed by Royal College of Physicians
   - Royal College of Ophthalmologists
   - Polymyalgia Rheumatica & Giant Cell Arteritis UK
   - Vasculitis UK

   The Department of Heath submitted a "No Comment" response

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Justin Mason – Clinical Expert, nominated by Roche

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Appendix of new evidence** – submitted by Roche

6. **Evidence Review Group critique of company ACD comments** - prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Tocilizumab for treating giant cell arteritis

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Clinical expert	Justin Mason	Overall I found the report accurate and well-balanced. Thank you for the opportunity to comments I have a few points to raise:	Thank you for your response.
2	Clinical expert	Justin Mason	Although I take on board the excellent modelling work done, my immediate response to the cost-effectiveness estimate for tocilizumab of at least £65,800 per QALY is why this is so much higher than for the same drug for rheumatoid arthritis. Although I fully accept I have no skills in financial modelling, the QALY makes me concerned regarding whether we have modelled its use in GCA correctly? I accept this is very difficult indeed but I think this requires further consideration in any future appraisals.	Comment noted. The committee explained that giant cell arteritis and rheumatoid arthritis are two different conditions with different clinical features and treatment requirements. Sections 3.8 to 3.13 describe the approach to modelling in detail.
3	Clinical expert	Justin Mason	The report conveys the impression that GCA is a disease that needs new drug therapy, and that GCA patients represent a group at major risk of serious steroid side-effects. The main reason for decline at this stage is the cost. However, I think the importance of the steroid-sparing effect of tocilizumab (shown in the Stone et al paper NEJM 2017) has been somewhat over-looked in the report and needs further consideration. We know it is the cumulative dose of steroids that is most closely related to side-effects and the use of tocilizumab is likely to reduce this impact.	Section 3.1 of the FAD has been updated. The committee recognised the importance of the steroid-sparing effect of tocilizumab and it was fully considered by the committee when reaching its conclusion on the recommendation made in the Final Appraisal Determination (FAD, section 1.1).
4	Clinical expert	Justin Mason	The opinions obtained from experts and organisations including the BSR prior to the meeting recommended targeting of tocilizumab to high risk patients (pre-existing diabetes, CV disease, hypertension, osteoporosis etc) and to those with refractory disease. This is in contrast to prescribing the drug in all cases which was put forward to the Appraisal Meeting. In my opinion targeting to high risk groups is the way forward for the introduction of this important drug.	Comment noted. Subgroups were considered by the committee (FAD, section 3.2) Please note that tocilizumab is now recommended as a treatment option for people with relapsed or refractory giant cell arteritis (FAD, section 1.1).
5	Clinical expert	Justin Mason	One important aspect to consider looking forward is that if we 'lose' tocilizumab for the NHS over the next year or two, the impact on the provision of new treatments for GCA in the UK could be very serious. Such a decision might significantly impact future clinical trials or research in this area, in which no therapeutic progress has been made for more than 50 years. This reinforces the need to look for a more affordable use of tocilizumab in GCA.	Comment noted. Subgroups were considered by the committee (FAD, section 3.2). Please note that tocilizumab is now recommended as a treatment option for people with relapsed or refractory giant cell arteritis (FAD, section 1.1).
6	Clinical expert	Justin Mason	The duration of treatment in this disease is extraordinarily difficult to predict or model. I don't think the statement that 'tocilizumab treatment is likely to exceed 2 years' strictly reflects discussion at the meeting or input from experts prior to the meeting. The most	Comment noted. The committee discussed a 1 year stopping rule and concluded that it was appropriate (FAD, section 3.9)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			widely held view was that treatment would typically be for 18-24 months. Although some may exceed two years, my own opinion is that this would be relatively small – maybe 10-15 %. Furthermore, as the GiActa trial showed a significant benefit following one year of therapy, I think most rheumatologists would accept a limit of one year's therapy if this was the only way in which the drug can be introduced within the understandable economic restrictions we all have to work within.	
7	Company	Roche	**GCA pathophysiology: the burden on patients and the NHS** **1.1 Appraisal reference** In Section 3.1 of the ACD, NICE states: "Giant cell arteritis causes inflammation in the walls of the arteries in the head and neck, and less commonly the aorta (known as large vessel giant cell arteritis). The patient experts explained that this causes symptoms such as headache, jaw pain, fatigue and muscle and joint pains. More serious complications include vision loss and stroke, and it is with visual symptoms that people often first present to health services." **1.2 Key points** • Roche consider that the severity of GCA pathophysiology has not been represented to its full extent in the ACD. We request that this be addressed by the Committee in its reconsideration of the evidence • Vascular inflammation and ischaemia can result in serious clinical sequelae such as vision loss, stroke, aortic aneurysm and dissection, and myocardial infarction • Newly published literature confirms that a wide variety of underlying co-morbidities are more common in patients with GCA than reference populations, including cardiovascular diseases, rheumatologic diseases, osteoporosis, severe infections and diabetes • Hospitalisation rates among GCA patients are significantly increased, compared to matched controls • The above considerations are discussed in relation to the economic model in Comment 8.8 **1.3 Clinical features of GCA** Roche considers that the severity of GCA pathophysiology has not been represented in its full extend in the ACD. GCA is characterised by a wide range of cranial and systemic manifestations including headache, fever and polymyalgia rheumatica. In some cases, a variety of severe ischemic symptoms can occur, of which the most important are ocular manifestations and stroke. Visual impairment and permanent vision loss are particularly dreaded complications of GCA (Dejaco et al. 2017; Kermani et al. 2017; Bukhari 2017; Koster et al. 2018). Additionally, vascular inflammation may lead to large-vessel complications such as arterial	Comment noted. The committee recognised the severity of giant cell arteritis pathophysiology and section 3.1 of the FAD has been amended to include the more serious complications of the condition. Moreover, the additional evidence submitted by the company and the severity of giant cell arteritis pathophysiology were fully considered by the committee when reaching its conclusion on the recommendation made in the Final Appraisal Determination (FAD, section 1.1)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			stenosis, vascular occlusion, myocardial infarction, aortic aneurysm, aortic dissection and upper limb ischaemia (Dejaco et al. 2017; Mohammad et al. 2017; Kermani et al. 2017; Koster et al. 2018). Clinical experts consulted for this response advise that the current cost to the NHS of managing GCA is high, particularly for those patients with ischaemic and/or large vessel complications. Likewise, the quality-of-life cost for patients and their carers is significant. **1.4 Co-morbidities in GCA** Elderly patients with GCA treated with high doses of corticosteroids are bound to have multiple medical problems. This has been quantified in a population-based cohort study of biopsy-proven GCA patients (Mohammad et al. 2017) which was not incorporated in our original submission. Specifically, they studied the frequency of comorbidities among 768 patients with GCA and compared rates to a reference group of 3,066 reference population patients. An increased relative risk (RR) of comorbidities was found for: • Osteoporosis: RR 2.81, 95% CI 2.33–3.37 • Venous thromboembolic diseases: RR 2.36, 95% CI 1.61–3.40 • Severe infections: RR 1.85, 95% CI 1.57–2.18 • Thyroid diseases: RR 1.55, 95% CI 1.25–1.91 • Cerebrovascular accidents: RR 1.40, 95% CI 1.12–1.74 • Diabetes mellitus: RR 1.29, 95% CI 1.05–1.56 • Ischemic heart disease: RR 1.20, 95% CI 1.00–1.44; NS These results are similar to those of previously reported increased rates of stroke, myocardial infarction, and peripheral vascular disease among patients with GCA in a large UK-based population (Petri et al. 2015). The comorbidities associated with GCA versus matched patients receiving steroid treatment were summarised following an extensive analysis of the UKs primary research database, the Clinical Practice Research Database (Table 1). **Table 1: Comorbidities associated with GCA versus matched patients receiving steroid treatment (Wilson et al. 2017)**	

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Characteristics	GCA group, $n = 5011$	Non-GCA group, $n = 5011$	χ^2
Comorbidity			
Rheumatologic disease	1090 (21.8)	274 (5.5)	**< 0.0001**
Polymyalgia rheumatica	911 (18.2)	127 (2.5)	**< 0.0001**
Renal disease	446 (8.9)	358 (7.1)	**0.0012**
Peripheral vascular disease	296 (5.9)	224 (4.5)	**0.0012**
Peptic ulcer disease	299 (6.0)	245 (4.9)	**0.0173**
Myocardial infarction	305 (6.1)	255 (5.1)	**0.0297**
Mild liver disease	1 (0.02)	2 (0.04)	0.5636
Moderate liver disease	32 (0.64)	12 (0.24)	**0.0025**
Hemiplegia	25 (0.5)	21 (0.4)	0.5544
Diabetes	516 (10.3)	484 (9.7)	0.2862
Diabetes with complications	119 (2.4)	105 (2.1)	0.3441
Dementia	32 (0.6)	58 (1.4)	**0.0003**
Congestive heart disease	300 (6.0)	228 (4.6)	**0.0013**
Chronic pulmonary disease	1249 (24.9)	952 (19.0)	**< 0.0001**
Cerebrovascular disease	521 (10.4)	376 (7.5)	**< 0.0001**
Average number comorbidities	1.03	0.70	–

1.5 Hospitalisation rates

The 2017 CPRD analysis (Wilson et al. 2017a) reported that the hospitalisation rate among GCA patients was significantly increased, compared to matched controls (Incidence Rate Ratio of 1.7, with 95% confidence interval of 1.6 - 1.8).

The most common causes of hospitalisation in the GCA group were diseases of the cardiovascular system, closely followed by diseases of the digestive system and of the eyes. It appears likely that this observation reflects both steroid-related AEs and the pathophysiology of GCA, in which increased risks for cardiovascular disease and vision impairment have been observed independently of glucocorticoid use.

1.6 Summary

Roche considers that the severity of GCA pathophysiology has not been represented to its full extent in the ACD. The management of large-vessel and ischaemic complications of GCA, in particular, are costly and resource heavy. This position is supported by newly published literature and expert clinical opinion.

Consequently, the current burden on patients, their carers and NHS resources is not comprehensively described in the ACD. This therefore diminishes the positive benefits that tocilizumab can provide. We request that this be addressed by the Committee in its reconsideration of the evidence.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Further amendments to the cost-effectiveness model have been made to incorporate more granular disease management costs (see Comment 8).	
8	Company	Roche	**<u>Patient sub-populations: identifying the greatest unmet need</u>** **2.1** Appraisal reference In Section 3.2 of the ACD, NICE states: "People with relapsing disease are usually offered lower doses of corticosteroids in an attempt to manage flares and minimise additional steroid exposure; as such, the clinical experts considered that tocilizumab would be most valuable to people with relapsing disease." **2.2 Key points** • Patients with relapsed or refractory GCA have the highest unmet need • Other subgroups are not able to be robustly analysed with current evidence • The amended cost-effectiveness model in Comment 8 is targeted to relapse/refractory GCA patients **2.3 Relapsed and refractory patients** Roche agrees with the Committee that tocilizumab would be most valuable for patients with relapsing or refractory GCA. However, we consider that the rationale for this has not been fully elucidated in the ACD. Primarily, relapsed/refractory patients are likely to have: (Stone et al. 2017; Wilson et al. 2017; Research Partnerships 2017) • sub-optimally treated disease, by definition • pre-existing high cumulative steroid burden • greater concomitant medication usage • higher body weight • greater burden of comorbidities This position is supported by the expert clinicians and patient organisations consulted by NICE in advance of the Appraisal Committee Meeting (https://www.nice.org.uk/guidance/gid-ta10172/documents/committee-papers). In response to question 11 of the consultation, the patient organisation PMRGCA stated: "People who might benefit more [from tocilizumab]: a) People with pre-existing conditions such as diabetes, hypertension, for whom long-term glucocorticosteroids are contra-indicated b) People who have exhibited an intolerance to steroids, such as steroid psychosis. c) People who are at work, or who have significant caring responsibilities or other factors making it more likely that they will experience 'flares' or relapses d) People with an existing history of relapse or flare, requiring them to increase their dose of GCs back up to the level of a previous dose." In response to question 12 of the consultation, the BSR stated: "All patients with relapsing disease and disease refractory to >15mg prednisolone/day will be greatly benefited from this drug. Those with steroid psychosis, congestive cardiac failure, brittle diabetes etc	Comment noted. The committee acknowledged the response from the company and other consultees and considered the new analyses submitted by the company (FAD, section 3.2). The recommendation made in the final appraisal determination (FAD, section 1.1) is made in respect of the full evidence base.

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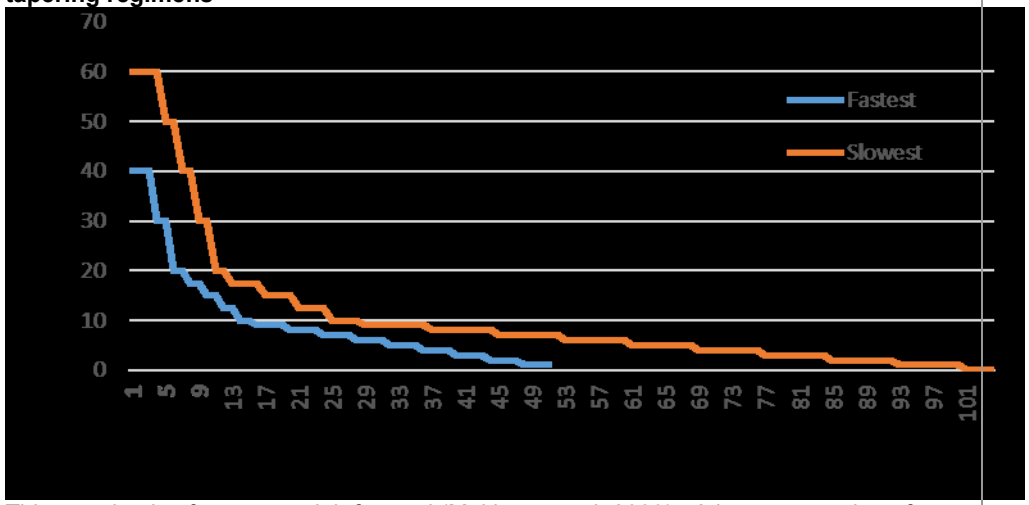
			(contraindications to high dose prednisolone therapy) will benefit greatly." Further, subgroup analysis was previously provided for the relapsed/refractory population, which was discussed in the Appraisal Committee Meeting, but was not reported in the ACD. **2.4 Other potential subgroups** Roche agrees with the Committee that there may be other relevant subgroups of patients with GCA, as described in Section 3.2 of the ACD, for example large-vessel GCA. Roche considers that there is also clinical plausibility for a subset of patients with newly-diagnosed GCA for whom tocilizumab would be valuable. Specifically, those who cannot tolerate glucocorticoids and those who are at high risk for steroid-related AEs (Bukhari M, 2017). For example, patients with pre-existing: • high cardiovascular risk • osteoporosis or osteopenia • obesity • diabetes However, robust evidence demonstrating efficacy in these sub-groups is lacking, due to small patient numbers. We have concerns about the interpretation of any such analyses as they would not be sufficiently powered to report any meaningful differences. **2.5 Summary** Roche agrees that the relapsed/refractory patient population would derive the most benefit from treatment with tocilizumab and would be the most responsible use of NHS resources. This position is supported by recently-published literature and the opinions of clinical experts and patient organisations. Likewise, this is the preferred assumption of the NICE ERG. Therefore, our revised economic model, described in Comment 8, reports the cost-effectiveness of tocilizumab for only patients with relapsed/refractory disease.	
9	Company	Roche	**Treatment goal in GCA: reduction in cumulative steroid burden** **3.1 Appraisal reference** In Section 3.1 of the ACD, NICE states: "People would welcome a new treatment that reduces the cumulative amount of steroids needed." **3.2 Key points** • Roche agrees that reduction in cumulative steroid burden is a valid and clinically significant treatment goal • UK clinical experts treating GCA consulted for this ACD response support this • However, this has not been reflected in subsequent parts of the ACD and therefore, Roche requests that this be addressed by the Committee in its reconsideration of the evidence	Comment noted. The committee recognised the treatment goal in giant cell arteritis and the importance of the steroid-sparing effect of tocilizumab have been accurately represented in the ACD. It also acknowledged that no new evidence was submitted by the company in the ACD response to further support this. The treatment goal of tocilizumab was fully considered by the committee when reaching its conclusion on the recommendation made in the final appraisal determination (FAD, section 1.1).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			3.3 Discussion Roche and clinical experts agree that reduction in cumulative steroid burden is a legitimate and important clinical aim in GCA. This is elucidated further below (Comments 4 and 5) and underscores the substantial unmet need for alternative treatment options for GCA. This aim validates the important steroid-sparing effect of tocilizumab in GCA patients, as demonstrated in the GiACTA study. Therefore, Roche considers that this highlights the urgency of making tocilizumab available to GCA patients in the UK. We request that this treatment goal be clearly reflected in the Committee's reconsideration.	
10	Company	Roche	**<u>Current standard of care: steroid tapering regimens</u>** **4.1 Appraisal reference** In Section 3.5 of the ACD, NICE states: "The committee was concerned that 52 weeks (12 months) is the minimum steroid taper recommended in the British Society for Rheumatology guidelines. The clinical experts explained that in clinical practice, corticosteroids would usually be tapered over 18 to 24 months. The committee considered that this might mean that the number of flares in the comparator arm (that is, placebo with 52-week steroid taper) may be higher, and the time to first flare shorter, than in clinical practice in England. The committee was also aware that 49% of patients in the comparator arm did not have disease remission after the 6 week screening phase of the trial, but that nonetheless they had to start the 52-week tapering regimen. The committee was concerned that this might bias the primary end point of the trial (sustained remission at 52 weeks) in favour of tocilizumab, because it is less likely that people whose disease has not responded to high-dose steroids would achieve remission with lower doses. The committee concluded that the 52-week steroid taper arm of the trial does not reflect clinical practice in England and might bias the results in favour of tocilizumab." **4.2 Key points** • Roche and clinical experts agree that tapering steroids over 52 weeks, as the 'fastest' BSR recommended regimen, may not reflect current real world clinical practice in the NHS • We have addressed this in the updated cost-effectiveness calculations, see Comment 8.4. **4.3 UK clinical guidelines** The BSR Guidelines (2010) suggest the following tapering regimen (assuming no GCA relapse): • 40–60mg prednisolone continued until symptoms and laboratory abnormalities resolve (at least 3–4 weeks); • then dose is reduced by 10mg every 2 weeks to 20 mg; • then by 2.5mg every 2–4 weeks to 10 mg; and • then by 1mg every 1–2 months provided there is no relapse.	Comment noted. Please see sections 3.5 and 3.15 of the final appraisal determination (FAD) for the committee's full considerations on the company's additional analyses of primary endpoint analysed by remission status and the proposed amendments to the steroid tapering arm, respectively.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			For illustrative purposes, Roche has mapped what the 'fastest' possible and 'slowest' possible BSR tapering regimens look like (Figure 1). **Figure 1: BSR treatment guidelines for GCA patients give a range of glucocorticoid tapering regimens**  This tapering is often not straightforward (Mukhtyar et al. 2009). A large proportion of patients (30-50%, Muratore et al. 2013) will experience relapse or flare upon steroid taper, most within the first few months after diagnosis and usually at a daily dose of 5-10 mg (Chandran et al. 2015). This necessitates a further increase in steroid dose to regain disease control. Cessation of steroids may take up to two years. **4.4 Clinical opinion** Roche has consulted clinical experts to clarify the most common steroid taper regimen in current UK clinical practice. They advised that, although the 52-week taper is recommended in the guidelines, this is often not achievable in real world clinical practice. Many patients relapse during the taper and require an increase in dose, which inevitably extends the overall taper period. For patients treated with tocilizumab, clinical experts have expressed support for the 26-week steroid tapering regimen, in alignment with the results of the GiACTA trial. **4.5 GiACTA baseline remission status** Although 49% of patients in the comparator arm were not in disease remission after the 6 week screening phase, a new exploratory analysis showed no difference in primary endpoint when analysed by remission status at baseline (Table 2).	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Table 2:Exploratory analysis of primary endpoint analysed by remission status
<table>
<tr><th></th><th colspan="2">Sustained remission at week 52</th></tr>
<tr><th></th><th>Remission at BL</th><th>No Remission at BL</th></tr>
<tr><td>PBO+52</td><td>19.2%</td><td>16.0%</td></tr>
<tr><td>TCZ QW</td><td>60.0%</td><td>52.3%</td></tr>
<tr><td>Delta (TCZ – PBO)</td><td>40.8</td><td>36.3</td></tr>
</table>
Source: Stone et al. 2017

4.6 Summary
Roche and clinical experts agree with the Committee that tapering steroids over 52 weeks is the fastest recommended regimen, and may not reflect real world clinical practice in the NHS.

Therefore, we have revised the prednisone-only arm of the cost-effectiveness model, to incorporate the slowest steroid taper regimen recommended by the BSR Guidelines.</td><td></td></tr>
<tr><td>11</td><td>Company</td><td>Roche</td><td><u>Steroid-related adverse events: the seriousness is understated</u>

5.1 Appraisal reference
In Section 1 of the ACD, NICE states: “Giant cell arteritis is usually treated with a high dose of corticosteroids, which is gradually reduced over time. High doses of corticosteroids may cause skin problems and weight gain, and long-term use can lead to diabetes and osteoporosis.”

5.2 Key points
• Roche considers that the ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients. We request that this be addressed in the Committee’s reconsideration of tocilizumab
• The seriousness of steroid-related AEs has been clearly described in the literature, including recently-published reviews of the evidence in GCA patients
• There are clear correlations between increasing harm and increasing average daily dose, as well as increasing cumulative steroid dose
• The EULAR taskforce recommends that at ≤5 mg/day steroids there is an acceptably low level of harm
• To more accurately represent this position, more granularity has been applied to the cost-effectiveness model, as described in Comment 8

5.3 Seriousness of steroid-related adverse effects
While Roche appreciates that steroids are the current mainstay of treatment for patients with GCA, steroid-related AEs and morbidity are common and potentially serious.
The seriousness of these AEs has been clearly reiterated in multiple recently-published and in-press reviews of the evidence which have not previously been taken into account by NICE (Dejaco et al. 2017; Kermani et al. 2017; Bukhari 2017; [redacted]</td><td>Comment noted. The committee recognised the seriousness of steroid-related adverse events and considered this to have been accurately reflected in the ACD. In addition, the steroid-related adverse events and evidence from new sources provided by the company as well as comments from consultees were fully acknowledged and considered by the committee (FAD, section 3.1) when reaching its conclusion on the recommendation made in the final appraisal determination (FAD, section 1.1).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Kermani et al. (2017) undertook a longitudinal study to assess damage in patients with GCA. After a median observation of 3.5 years, >80% of patients with GCA had at least one item of damage. New items of damage were observed in more than half of the patients in this cohort, with the majority being related to treatment. They conclude that "Better therapeutics for GCA that target disease activity and reduce the cumulative burden of disease- and treatment-associated damage are needed." [redacted] Other published evidence shows 86% of GCA patients experience steroid-related AEs after 10 years of follow-up. Serious AEs include bone fractures, hip necrosis, diabetes, infections, gastrointestinal bleeding, cataracts, hypertension, skin-thinning and hirsutism (Nesher, Sonnenblick, and Friedlander 1994; Proven et al. 2003; Petri et al. 2015; Broder et al. 2016). For the purposes of this response, Roche sought additional data specific to steroid-related AEs. In 2011, Sarnes et al. published a systematic review of the incidences of and risks for AEs associated with oral and parenteral corticosteroids in the general US population (Table 3). Forty-seven studies were included. Across patient populations, the most frequently reported corticosteroid-associated AEs were psychiatric events, infections, gastric conditions, and fractures. Corticosteroid-associated AEs reported to occur at an incidence >30% were sleep disturbances, lipodystrophy, adrenal suppression, metabolic syndrome, weight gain, and hypertension. Vertebral fractures were reported at an incidence of 21% to 30%. Table 3 shows the AEs categorised by risk measure (including hazard ratios, incidence risk ratios, relative risks, and odds ratios) across patient populations. The time frames over which risks were characterised varied among studies. Only AEs with a significant difference between patients who received corticosteroids and those who did not receive corticosteroids are listed. AEs having a strong association with corticosteroid therapy were	

<table>
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<tr><td></td><td></td><td></td><td>fractures, cardiovascular disorders and events, gastrointestinal disorders and events, and infections.

Table 3: GC-related AEs reported in the literature, including the highest reported risk ratio
<table>
<tr><th>Steroid-related AEs in any population</th><th>Highest reported risk ratio</th></tr>
<tr><td>Any fracture</td><td>3 - <5</td></tr>
<tr><td>Back pain</td><td>1 - <2</td></tr>
<tr><td>Bacterial sepsis</td><td>1 - <2</td></tr>
<tr><td>Basal cell carcinoma</td><td>1 - <2</td></tr>
<tr><td>Bladder cancer</td><td>2 - <3</td></tr>
<tr><td>Bleeding</td><td>1 - <2</td></tr>
<tr><td>Bruising</td><td>≥5</td></tr>
<tr><td>Cataracts</td><td>≥5</td></tr>
<tr><td>Cushingoid phenotype†</td><td>≥5</td></tr>
<tr><td>Diabetes</td><td>1 - <2</td></tr>
<tr><td>Ecchymosis</td><td>≥5</td></tr>
<tr><td>Epistaxis</td><td>≥5</td></tr>
<tr><td>Gastric damage</td><td>2 - <3</td></tr>
<tr><td>Gastric lesions/ulcer‡</td><td>≥5</td></tr>
<tr><td>GI hemorrhage</td><td>1 - <2</td></tr>
<tr><td>Height loss of 2.5 cm</td><td>1 - <2</td></tr>
<tr><td>Hip/femur fracture§</td><td>≥5</td></tr>
<tr><td>Hospitalization for atrial fibrillation or flutter</td><td>≥5</td></tr>
<tr><td>Hypertension</td><td>2 - <3</td></tr>
<tr><td>Hypokalemia</td><td>1 - <2</td></tr>
<tr><td>Infection</td><td>2 - <3</td></tr>
<tr><td>Leg edema</td><td>2 - <3</td></tr>
<tr><td>Lethal infection</td><td>≥5</td></tr>
<tr><td>Mental status change</td><td>≥5</td></tr>
<tr><td>Muscle weakness</td><td>≥5</td></tr>
<tr><td>Myocardial infarction</td><td>2 - <3</td></tr>
<tr><td>Non-Hodgkin’s lymphoma</td><td>2 - <3</td></tr>
<tr><td>Nonlethal infections</td><td>2 - <3</td></tr>
<tr><td>Oral candidiasis</td><td>≥5</td></tr>
<tr><td>Osteonecrosis of femoral head¶</td><td>≥5</td></tr>
<tr><td>Parchmentlike skin</td><td>3 - <5</td></tr>
<tr><td>Peptic ulcer‡</td><td>1 - <2</td></tr>
<tr><td>Ribs/sternum fracture</td><td>3 - <5</td></tr>
<tr><td>Sleep disturbance</td><td>1 - <2</td></tr>
<tr><td>Squamous cell carcinoma</td><td>≥5</td></tr>
<tr><td>Tuberculosis#</td><td>≥5</td></tr>
</table></td><td></td></tr>
</table>

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Ulcers	3 - <5
Upper GI complications	1 - <2
Upper limb fracture (not wrist)	2 - <3
Varicella infection	≥5
Vertebral fracture§	≥5
Weight gain	2 - <3

GI: gastrointestinal. *Only AEs with a statistically significant difference in risk between patients receiving corticosteroids and those not receiving corticosteroids are listed. Some studies may have been underpowered to detect significant differences. The risk ratio could reflect a hazard ratio, an incidence risk ratio, a relative risk, or an odds ratio. † Risk for Cushingoid phenotype increased with higher corticosteroid dose. ‡ Risk for gastrointestinal ulcers/lesions varied by study and appeared to increase with higher corticosteroid dose. § Risk for vertebral fracture and hip/femur fracture increased with higher corticosteroid dose and in certain patient populations (e.g. the elderly). Risk for infection varied by type of infection and by study. Risk for osteonecrosis of the femoral head varied by study and patient population. # Risk for tuberculosis varied by study.
Source: Sarnes et al. 2011

5.4 Impact of steroids on GCA patients' quality of life
Research by the GCA and PMR Charity Group, PMRGCAUK, found "coming off steroids" and "living with steroids" are highly important to individuals with GCA (www.pmrgca.co.uk). Steroid-related AEs are likely to be exacerbated in the GCA population who are predominantly females over 50 years old. They are likely to be suffering from pre-existing multiple co-morbidities which may pose relative or absolute contraindications to steroid therapy (Dejaco et al. 2017).

5.5 Assessing harm associated with steroid dose
The level of harm associated with steroid therapy depends on mean daily dose, total duration of intake and cumulative dose (Strehl et al. 2016; Harris et al. 2015; [redacted]).
Broder et al. (2016) have shown in a recent retrospective study, that for each 1,000 mg increase in cumulative glucocorticoid dose, the hazard ratio for AEs is increased by 3%. Wilson et al. 2017 provides robust evidence of the link between steroid dose and serious AEs. They described serious AEs associated with steroid therapy in patients with GCA in a nested case-control analysis from a large (n=5011) UK CPRD database. The majority of cases of diabetes, glaucoma, and osteoporosis occurred within 2 years following steroid treatment initiation, with over 40% of diabetes and glaucoma cases developing in the first year.
There was a clear trend of increasing risk with increasing average daily dose; GCA patients exposed to higher average daily prednisolone dose were at significantly increased risk of developing diabetes, glaucoma, osteoporosis, fractures, serious infections, and death compared to those with lower doses (Table 4).

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Hence, tocilizumab can be expected to bring clinical benefit to GCA patients, even over a period of time shorter than the length of active disease.

Table 4: Adjusted odds ratios for outcomes of interest according to average daily prednisolone dose in GCA patients

	Fractures			Osteoporosis			Infection			Death		
Average daily prednisolone dose (mg/d)[a]	Cases n = 408 (%)	Controls n = 1586 (%)	AOR (95% CI)[b]	Cases n = 511 (%)	Controls n = 1821 (%)	AOR (95% CI)[c]	Cases n = 433 (%)	Controls n = 1421 (%)	AOR (95% CI)[d]	Cases n = 517 (%)	Controls n = 1774 (%)	AOR (95% CI)[e]
≤5	88 (21.6)	409 (25.8)	1.00	79 (15.5)	391 (21.5)	1.00	76 (17.6)	310 (21.8)	1.00	113 (21.9)	478 (26.9)	1.00
>5 to ≤10	128 (31.4)	575 (36.3)	1.1 (0.8–1.5)	177 (34.6)	619 (34.0)	1.3 (1.0–1.8)	136 (31.4)	476 (33.5)	1.1 (0.8–1.6)	197 (38.1)	695 (39.2)	1.1 (0.8–1.5)
>10 to ≤20	119 (29.2)	394 (24.8)	**1.9 (1.3–2.6)**	148 (29.0)	329 (18.1)	**1.5 (1.1–2.2)**	105 (24.2)	390 (27.4)	1.3 (0.9–1.9)	123 (23.8)	374 (21.1)	1.4 (1.0–2.0)
>20 to ≤30	32 (7.8)	105 (6.6)	**2.0 (1.2–3.2)**	150 (29.4)	157 (8.6)	**1.7 (1.1–2.7)**	39 (9.0)	114 (8.0)	1.7 (1.0–2.7)	41 (7.9)	125 (7.0)	1.7 (1.0–2.8)
>30	41 (10.0)	103 (6.5)	**2.6 (1.6–4.3)**	57 (11.2)	172 (9.4)	**1.9 (1.2–2.9)**	77 (17.8)	131 (9.2)	**3.3 (2.2–5.2)**	43 (8.3)	102 (5.7)	**2.1 (1.3–3.5)**
p^{trend}			**<0.001**			**0.0020**			**<.0001**			**<0.001**

Diabetes			Glaucoma		
Cases n = 321 (%)	Controls n = 1272 (%)	AOR (95% CI)[f]	Cases n = 243 (%)	Controls n = 957 (%)	AOR (95% CI)[g]
55 (17.1)	280 (22.0)	1.00	39 (16.0)	187 (19.5)	1.00
75 (23.4)	436 (34.3)	0.9 (0.6–1.4)	74 (30.5)	344 (35.9)	1.1 (0.7–1.7)
73 (22.7)	350 (27.5)	1.2 (0.7–1.8)	59 (24.3)	275 (28.7)	1.1 (0.7–1.8)
38 (11.8)	105 (8.3)	**2.5 (1.4–4.3)**	24 (9.9)	76 (7.9)	1.6 (0.9–3.0)
80 (24.9)	101 (7.9)	**4.7 (2.8–7.8)**	47 (19.3)	75 (7.8)	**3.5 (2.0–6.1)**
		<0.001			**<0.001**

Values in bold are statistically significant. CI, confidence interval; AOR, adjusted odds ratio.

[a] The median range for total duration of prednisolone use (days) across all outcomes for cases and controls respectively was 765–1302 and 528–994 for <5 mg, 625–1152 and 656–941 for >5 to ≤10 mg, 347–607 and 364–470 for >10 to ≤20 mg, 109–226 and 112–154 for >20 to ≤30 mg, 43–74 and 20–50 for >30 mg.

[b] Adjusted for smoking status, BMI, osteoporosis, vision disturbances, epilepsy, dyspepsia, dementia, vitamin D supplementation, steroid injection, past prednisolone prescription, and GCA duration.

[c] Adjusted for alcohol status, smoking status, BMI, COPD, past history of fractures, calcium supplementation, immunosuppressant use, and GCA duration.

[d] Adjusted for alcohol status, smoking status, BMI, diabetes, cardiovascular disease, COPD, and GCA disease duration.

[e] Adjusted for alcohol status, smoking status, BMI, COPD, stroke, cardiovascular disease, sepsis, diabetes, pneumonia, ulcer, epilepsy, dementia, thrombocyte aggregation inhibitor use, vitamin K use, proton pump inhibitor use, nitrate use, and GCA duration.

[f] Adjusted for alcohol status, smoking status, BMI, COPD, stroke, bisphosphonate use, coronary vasodilator use, vitamin K use, statin use, and GCA duration.

[g] Adjusted for BMI, ocular steroid use, history of thrombocyte aggregation inhibitors use, beta blocker use, insulin treatment, and GCA duration.

Source: Wilson et al. 2017

With regard to mean daily dose, a 2015 EULAR task force considered that for long-term steroid use (3- 6 months or more): (Strehl et al. 2016)

- At ≤5 mg/day, there is an acceptably low level of harm for the specified outcomes (with the exception of patients at high risk for CVD who may require preventive measures)
- At >10 mg/day, the risk of harm is high
- At dosages between >5 and ≤10 mg/day, uncertainty still exists and, consequently, patient-specific characteristics need particular consideration to interpret and estimate the individual risk of harm

This reiterated in the in-press Buttgereit et al (2018) review of the evidence.

5.6 Steroid doses in GCA

Patients with GCA generally require higher starting doses and longer duration of steroid therapy than patients with other systemic inflammatory diseases ([redacted])
Indeed, recent US claims-based data suggest that patients with GCA typically receive cumulative glucocorticoid doses of >5,000 mg prednisone-equivalent over the course of several years (Broder et al. 2016).
A similar large UK database of 3,074 patients with GCA demonstrated that 33% of patients were treated with a cumulative dose of prednisone >10,000 mg (Petri 2015).

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			Trends in recent decades for steroid use in GCA also suggest increasing cumulative doses and longer exposures (Chandran et al. 2015; [redacted]). Patients with refractory disease are by definition poor responders to steroids, with frequent relapse and flare. As such they require much higher and prolonged courses whilst an effective steroid-sparing agent is sought, with higher cumulative doses. This further validates our position in Comment 2. **5.7 Summary** Roche considers that the ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients. This position is supported by recently published literature and expert clinical opinion. Roche requests that this be reflected in the Committee's reconsideration of the evidence. There are clear correlations between increasing harm and increasing average daily steroid dose, as well as increasing cumulative steroid dose. At ≤5 mg/day, there is an acceptably low level of harm. This has been considered further in our economic model in Comment 8. Nevertheless, it is challenging to incorporate many steroid-related AEs into the cost-effectiveness model. On this basis, Roche requests that NICE takes into account that the modelled ICER is likely to be an overestimate.	
12	Company	Roche	**<u>Clinical effectiveness of tocilizumab: impact on steroid-related toxicities</u>** **6.1 Appraisal reference** In Section 3.7 of the ACD, NICE states: "Because tocilizumab is taken with corticosteroids, the extent to which steroid-related adverse events are reduced is unclear. One of the main perceived benefits of tocilizumab is a reduction in cumulative steroid dose and risk of steroid-related adverse events. The committee noted that although the initial tapering regimen with tocilizumab is shorter than when corticosteroids are used alone, disease flare ups are treated by increasing the steroid dose, and a tapering regimen restarted. As such, people taking tocilizumab could still be exposed to large cumulative doses of corticosteroids. The committee acknowledged that the median cumulative steroid dose was lower in the tocilizumab arm of GiACTA (see table 1), but noted that this was over the relatively short 52-week follow-up. It was concerned that despite the lower median cumulative steroid dose in the tocilizumab arm, the rate of steroid-related adverse events was similar between arms (50% vs. 49%). The committee concluded that because corticosteroids still need to be taken with tocilizumab, the extent to which steroid-related adverse events are reduced is unclear." **6.2 Key points** • Roche considers that there is robust clinical evidence for the impact of tocilizumab on cumulative steroid burden, and therefore steroid-related AEs. We request that this be reflected in the Committee's reconsideration of the evidence. • GiACTA shows that tocilizumab enables a clinically significant >50% reduction in	Comment noted. Please see section 3.7 of the final appraisal determination (FAD) for the committee's full considerations on the company's additional analyses on the impact of steroid-related toxicities.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			cumulative steroid burden over 52 weeks, achieved through: ○ more rapid steroid taper ○ reduction in the rate of flare • Post-hoc analysis has shown that patients on the placebo arms of GiACTA had [redacted] **6.3 Reduction in cumulative steroid burden in GiACTA** Roche agrees with the Committee that one of the main benefits of tocilizumab therapy is the reduction in cumulative steroid dose; this is achieved by both allowing a rapid taper of steroid and by decreasing the flare rate (Stone et al. 2017; Bukhari, M. 2017; [redacted]). However, Roche disagrees that the "extent to which steroid-related adverse events are reduced is unclear". Over the 52-week duration of GiACTA there was >50% reduction in cumulative steroid burden for patients taking tocilizumab. • 1,862 mg for tocilizumab + 26-week steroid taper • 3,818 mg for placebo + 52-week steroid taper Given that there is a 3% increase in relative risk of AEs with each gram of cumulative steroid (see Comment 5 above; Broder et al. 2016), the difference seen in GiACTA is highly clinically relevant. This is especially urgent in the light of the data by Petri et al (2015) showing that over one third of UK GCA patients have been exposed to >10,000 mg of steroids, with all the inherent risks this poses. **6.4 Rapidity of steroid taper** Roche would like point out that many patients on tocilizumab can taper to zero steroid within six months, after which they are managed on tocilizumab monotherapy. As discussed in Comment 4.5, for patients treated with tocilizumab, clinical experts have expressed support for the 26-week steroid tapering regimen, in alignment with the results of GiACTA. **6.5 Rate of steroid-related AEs in GiACTA** Roche considers that there are valid explanations for the similar rate of steroid-related AEs in the GiACTA arms (50% vs. 49%), despite the lower median cumulative steroid dose in the tocilizumab arm. Firstly, GiACTA was not designed to fully ascertain the long-term steroid-sparing benefit of tocilizumab, or the safety events related to steroid use, since this would require trials of considerable duration. Further, it is important to note that many steroid-related AEs manifest in the longer-term, and therefore we would not expect to see significant differences over the course of the 52-week study. Additionally, the steroid-related AEs reported in our original submitted dossier (Table 5) are (S)AEs considered related to blinded study treatment by the investigator. The investigators made clinical judgements without knowing the arm of the study the patient	

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was in.

Table 5: Adverse events in GiACTA by arm and by investigator judgment of relatedness

Study arm	SAEs at Week 52 (none were fatal) (numerically higher for PBO)	AEs/100 patient years (numerically higher for PBO)	AEs related to blinded treatment	SAEs related to blinded treatment
PBO+26	22%	990.8	64%	14%
PBO+52	25.5%	1011.2	53%	12%
TCZ QW	15%	872.0	68%	6%
TCZ Q2W	14.3%	948.0	74%	4%

To validate these findings, Roche has since undertaken a further analysis of GiACTA to determine which AEs could be considered related to steroid use. These data have not previously been considered by NICE. It is important to note that these data were analysed retrospectively and were not based on standard or pre-specified criteria.
Events that were consistent with steroid-induced toxicity from Part 1 of GiACTA [redacted] These included [redacted]
The results show [redacted] of steroid-induced toxicity events being seen in the placebo + 52 week taper arm and [redacted] being seen in the tocilizumab QW arm. This post-hoc analysis shows [redacted] (Table 6).

Table 6: Rates of steroid-related toxicity in post-hoc analysis of GiACTA

	Steroid-induced toxicity events
PBO+26	[redacted]
PBO+52	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td>TCZ QW</td><td>[redacted]</td></tr><tr><td>TCZ Q2W</td><td>[redacted]</td></tr></table> **6.6 Summary** Roche considers that there is robust clinical evidence for the beneficial impact of tocilizumab on cumulative steroid burden, and therefore steroid-related AEs. We request that this be reflected in the Committee's reconsideration of the evidence. As described in Comment 5, it has been proven that steroids are clearly associated with a range of serious adverse events. Further, there is a robust body of evidence linking dose and cumulative steroid burden to increased risk of harm, as described in Comment 5. Reduction in cumulative steroid burden is a clinically valid treatment goal, as discussed in Comment 2. GiACTA showed that tocilizumab reduces the cumulative steroid dose for patients by >50%, as well as reducing the flare rate. Consequently, it is logical to expect a subsequent reduction in harm and clinically significant benefit for patients taking tocilizumab. [redacted] Therefore, we consider that making tocilizumab available on to GCA patients in the UK would be a rational use of NHS resources.	
13	Company	Roche	**Duration of tocilizumab treatment: 12 months of tocilizumab is efficacious and cost-effective** **7.1 Appraisal reference** In Section 3.9 of the ACD, NICE states: "The company assumed in their economic model that treatment with tocilizumab stops after 2 years. However, the committee was concerned that in clinical practice treatment may continue well beyond 2 years. This is because the risk of relapse continues, and there is no evidence that tocilizumab modifies the underlying disease when treatment stops (it may just supress it for the duration of treatment). The committee was aware that in both the preliminary results of the GiACTA follow-up study and in a smaller phase II study (NCT01450137), around half the patients' disease relapsed after stopping tocilizumab. The clinical experts commented that if the disease was controlled after 2 years of treatment, the interval between treatments could potentially be increased. In addition, tocilizumab treatment may be stopped and only restarted in the event of a relapse." **7.2 Key points** • Roche and clinical experts consider that 12 months tocilizumab treatment would provide clinically relevant efficacy and be a responsible use of NHS resources. We request that the Committee's reconsideration reflects this stance	Comment noted. Please see section 3.9 of the final appraisal determination (FAD) for the committee's full considerations on the duration of tocilizumab treatment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• GiACTA has shown that 12 months of tocilizumab is highly effective in sustaining remission and reducing cumulative steroid burden • In a new review of published case series', the majority of patients received tocilizumab for much less than one year (range 1 to 53 months) • For those patients who are unable to taper to 0 mg steroid in 52 weeks, expert clinicians and international clinical guidelines agree 5-7.5 mg/day to be an acceptable maintenance steroid dose • Consequently, our revised cost-effectiveness model incorporates 12 months of tocilizumab therapy for relapsed/refractory patients. **7.3 Expert clinical opinion** Upon consultation with expert clinicians, it has become clear that two years of tocilizumab treatment would not be required for the vast majority of patients. There is broad clinical support for reimbursing 12 months of tocilizumab, as a judicious use of NHS resources. Indeed, many patients would require less than 12 months of treatment to achieve sustainable remission, although this is difficult to quantify. **7.4 Sustained remission rates after 12 months of tocilizumab** In the GiACTA study, treatment with tocilizumab over 52 weeks was shown to be highly effective in sustaining remission and reducing cumulative steroid burden (Stone et al. 2017). In the previously provided Part 2 follow-up, although incomplete, [redacted] of patients who had previously been in either of the tocilizumab arms (or [redacted] of those on QW tocilizumab) were still in sustained remission once they had stopped taking study drug and who had reached Study Week 100 or beyond. This highlights that one year of treatment with tocilizumab is sufficient to sustain remission in the longer term and thereby reduces the steroid burden in these patients. The supporting data from Adler et al. (2016), reported in the our originally submitted dossier, also showed, albeit with very small numbers, that a substantial proportion of patients remained in remission after their last infusion of tocilizumab; 45% had not relapsed after a median follow-up time of 12.5 months. **7.5 Duration of treatment in case series'** Since the Committee meeting, Roche has undertaken a literature review of published case reports of the use of tocilizumab in GCA (undertaken on 23 November 2017; Evans et al., 2016; Loricera et al.; 2015, Regent et al., 2016; Aitisha & Fayad., 2015; Besada & Nosent, 2012; Beyer et al., 2011; Christidis et al., 2011; Işik et al., 2013; Kieffer et al., 2014; Lurati et al., 2012; Oliveira et al., 2014; Pazzola et al., 2013; Salvarini et al., 2012; Sciascia et al., 2011; Seitz et al., 2011; Unizony et al., 2012; Vinicki et al., 2017; Vinit et al., 2012; Vionnet et al., 2017). These were not provided in our original submission as they are considered a lower level of evidence than randomised data. Nevertheless, they offer useful insight and clear trends into the length of time patients have been treated with tocilizumab in the real world, and	

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			also the steroid doses deemed acceptable for maintenance by clinicians for GCA patients. In these published case reports, 109 patients with GCA had been treated with tocilizumab. The key findings were: • Most (99/109) patients received tocilizumab 8 mg/kg IV every 4 weeks (Q4W) but other doses were also used • The majority of patients (98/109) received tocilizumab in combination with steroids. The dosage of steroids at tocilizumab onset varied from zero to 60 mg/day • Positive treatment effects of tocilizumab were reported for the majority of patients with clinical efficacy observed between one and three months after the first tocilizumab infusion • Tocilizumab was administered for different time periods (range 1 to 53 months), the majority of patients receiving tocilizumab for much less than one year • During treatment with tocilizumab, steroid doses were reduced down, many from ~45-60 mg/day to ~5 mg/day (some down to zero mg/day). One of the larger studies (Regent et al. 2016), following 34 patients with tocilizumab treatment, reported a mean treatment time with tocilizumab of 6.4 ± 4.5 months with a median follow-up of 13 months (range 1-48). Treatment stopped in 23 patients after a mean treatment duration of 5.6 ± 2.9 months and only 34.8% experienced a flare after a mean of 3.5 ± 1.3 months. These reports validate that clinicians believe 5-7.5 mg/day to be an acceptable steroid dose to maintain patients on following treatment with tocilizumab. This is consistent with the EULAR taskforce (Strehl et al. 2016) as described in Comment 5. **7.6 Summary** Roche disagrees with the Committee that all patients would need to be treated with tocilizumab for two years or more. We consider that treatment with tocilizumab for up to 12 months would be highly beneficial for GCA patients, both in terms of inducing sustained remission and reducing cumulative steroid burden. This position is supported by expert clinical opinion, as a judicious use of NHS resources. We request that the Committee's consideration reflects this stance. Consequently, our revised cost-effectiveness model, described in Comment 8, incorporates 12 months of tocilizumab therapy for relapsed/refractory patients.	
14	Company	Roche	**Revision of the cost-effectiveness model** **8.1 Appraisal reference** In Section 3.14 of the ACD, NICE states: "The company's base-case deterministic incremental cost-effectiveness ratio (ICER) for the overall population was £28,272 per quality-adjusted life year gained (QALY). The ERG's base-case probabilistic ICER was £65,801 per QALY gained... The committee preferred the ERG's base-case estimate, because it reflected some of its preferred assumptions." "The ERG's base case did not address the uncertainties arising from the fact that the 52-week steroid taper used in the comparator arm of the trial does not reflect clinical practice in the NHS"	The company's additional evidence appendix was considered by the committee (FAD, section 3.14).

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			"Having concluded that the ICER is significantly higher than the range normally considered to be a cost-effective use of NHS resources, the committee did not recommend tocilizumab."
			
			8.2 Key points:
			• Roche has revised the cost-effectiveness model to incorporate new evidence and the interpretations of the clinical experts we have consulted
			• Using the ERG's model and preferred assumptions, the ICER for 12 months tocilizumab treatment for relapsed/refractory GCA patients is £30,528/QALY
			  o This was not reported in the Appraisal Consultation Document although it was considered during the Appraisal Committee Meeting
			• Roche identified 2 errors in the cost-effectiveness model, which have been amended
			• Further amendments to the cost-effectiveness model have been made to address questions raised in the Appraisal Committee Meeting, including:
			  o amending the steroid tapering regimen matching NHS practice
			  o incorporating more granular management costs from market research
			  o updating the costs of steroid-related AEs to 2017
			  o adjusting the ERGs flare rate to better reflect GiACTA data
			• These changes combined give an ICER of £18,898/QALY, including the confidential Patient Access Scheme
			
			The model amendments and associated ICER calculations presented in Appendix 1 are made using the Committee's preferred assumptions in the ERGs model for 12 months tocilizumab treatment in relapsed/refractory GCA patients. As discussed in Comments 2 and 7, relapsed/refractory patients have the highest unmet need in GCA, with the 12 months' treatment duration having the highest internal validity as this matches the GiACTA trial data.
			
			All ICERs presented in Appendix 1 include the confidential Patient Access Scheme (PAS) for tocilizumab.
			
			Summary
			Additional, relevant evidence has been incorporated into the cost-effectiveness model to support NICE in forming reasonable interpretations and sound and suitable guidance to the NHS regarding tocilizumab to treat GCA patients. This additional evidence gives an ICER of £18,898 for relapsed/refractory patients with 12 months of tocilizumab treatment.
			
			We trust that the information provided herein will allow NICE to reconsider its provisional recommendation and allow access to tocilizumab on the NHS.	

16	Patient/	The Royal	We are concerned that this preliminary recommendation has not fully taken into account	Comment noted. Please note that tocilizumab is

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	professional	College of Ophthalmologists	the current difficulty in managing those with severe relapsing and refractory Giant Cell Arteritis, particularly in those with extensive disease such as ischaemic complications and large vessel Giant Cell Arteritis.	now recommended as a treatment option for people with relapsed or refractory giant cell arteritis (FAD, section 1.1).
17	Patient/ professional	The Royal College of Ophthalmologists	We are concerned that this preliminary recommendation has not fully taken into account those who are diagnosed with Giant Cell Arteritis and have multiple co-morbid conditions such as Diabetes Mellitus, Osteopenia, Osteoporosis, Cardiovascular diseases and Glaucoma where treating with high dose glucocorticoids can be problematic and compound their existing premorbid conditions.	Comment noted. The committee recognised that people with giant cell arteritis are often above 50 years with additional health problems (FAD, section 3.1). . Please see section 3.2 of the final appraisal determination (FAD) for the committee's full considerations about subgroups.
18	Patient/ professional	The Royal College of Ophthalmologists	We are concerned that this preliminary recommendation has not fully taken into account those who are diagnosed with Giant Cell Arteritis who through the course of their disease have multiple-flares and are therefore at higher risk of an excessive cumulative glucocorticoid dose.	Comment noted. Please see section 3.2 of the final appraisal determination (FAD) for the committee's full considerations about subgroups.
19	Patient/ professional	The Royal College of Ophthalmologists	The breath of glucocorticoid toxicity is well documented in the literature. However, we are concerned that the economic modelling for the types of steroid induced adverse events may not be totally accounted for in the models here as they have not delineated those with refractory or relapsing disease who will have a higher cumulative glucocorticoid dose, than uncomplicated Giant Cell Arteritis. In the literature, the direct health care economic burden of complications induced by glucocorticoid use are excessive and in 2009 were estimated by *Mason SC et al* as at least an extra £84.2 million per year to the NHS. The majority listed below have profound health implications for the patient as well as the National Health Service: 1. Increase in weight and body mass index – obesity 2. Low mood, depression and depressive symptoms 3. Bone health – osteoporosis and fractures 4. Gastrointestinal – gastric ulcers 5. Ophthalmic complications – cataracts, ocular hypertension and glaucoma 6. Cardiovascular events- Hypertension and increased risk of myocardial infarction 7. Cerebrovascular events- increased risk of stroke and vascular dementia.	Comment noted. The committee considered that the model adequately captures the effects of glucocorticoids on quality of life (FAD, section 3.13) The ERG also noted that depression and weight gain are already captured in the "base" utility estimate and the estimates of disturbance (FAD, section 3.13).
20	Patient/ professional	The Royal College of Ophthalmologists	This preliminary recommendation has not been able to capture the increased direct health care costs of refractory disease; relapsing disease; manging co-morbidities and glucocorticoid toxicity or adverse events in Giant Cell Arteritis. Including increased admitted patient care, out-patient care, primary care and emergency care; surgery, in some; and increased length of stay in hospital.	Comment noted. The committee considered and accepted the company's updated model in relapsing and refractory disease only (FAD, section 3.15 and 3.16)
21	Patient/ professional	The Royal College of Ophthalmologists	We are concerned that this preliminary recommendation has not fully taken into account the patient voice from this disease group. Other vasculitic conditions have targeted treatments, and patients may not understand why they will not be afforded targeted therapy when the evidence exists that Tocilizumab has a cleaner safety profile than glucocorticoids, and has class 1 evidence (The GiACTA trial) that interleukin-6 inhibition is effective in treating Giant Cell Arteritis.	Comment noted. The committee fully considered the patient comments received in the response to the appraisal consultation document and the patient expert's views at both appraisal committee meetings. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in

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				respect of the full evidence base, including the perspective of the patient.
22	Patient/ professional	The Royal College of Ophthalmologists	We are concerned that this preliminary recommendation has not fully taken into account the patient voice from this disease group regarding their quality of life and their independence. Glucocorticoid adverse events have a negative effect on quality of life and independence.	Comment noted. The committee fully considered the patient comments received in the response to the appraisal consultation document and the patient expert's views at both appraisal committee meetings. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base, including the perspective of the patient.
23	Patient/ professional	The Royal College of Ophthalmologists	We are concerned that this preliminary recommendation could be seen as discriminating against those who are of older age. Giant Cell Arteritis has an increasing incidence with age and age may be a reason why, to date, there has been little quality clinical data. Older patients have a higher need of targeted therapy, as they have accumulated a higher number of co-morbidities. Completely rejecting a targeted treatment for any sub-type of Giant Cell Arteritis could be seen to discriminate based on age.	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1). The committee concluded that its recommendations do not have a different impact on people protected by equality legislation than on the wider population (FAD, section 3.18)
24	Patient/ professional	Polymyalgia Rheumatica & Giant Cell Arteritis UK	The committee recognises the point that Clinical trial results show that after having tocilizumab plus corticosteroids for 1 year, more people are able to sustain a remission and manage on lower doses of corticosteroids compared with people having corticosteroids alone. We feel that insufficient consideration has been given to the fact that glucocorticosteroids work by 'damping down' symptoms systemically, whereas TCZ operates directly on the interleukin IL-6 which is a major agent in the disease. By doing so, it is directly treating the disease, which can accelerate recovery, and which explains why rates of relapse are reduced. Therefore, the assumption that TCZ is likely to be used for as long as steroid medication by itself is erroneous. It is more likely that patients will be able to reduce their overall levels of medication and be able to come off medication completely after two years. Currently patients are told that they will be on steroids for two years, but the reality is that this period is generally much longer. This is because steroids do not treat the disease itself. Therefore we would consider it reasonable to prescribe TCZ for patients who have refractory disease in order for them to have a chance to reduce their dependency on prednisolone. If that dependency is not reduced within a year it would be reasonable to assume that TCZ is not working, in which case it would need to be withdrawn. As evidence we cite the 2012 study by Unizony et al, "Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica" .Arthritis Care Res (Hoboken). 2012 Nov;64(11):1720-9. doi: 10.1002/acr.21750. This study evidenced the clinical effects of TCZ in a group of refractory patients: "The mean	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1). Please see sections 1.1 and 3.9 of the final appraisal determination (FAD) for the committee's recommendation and full considerations on the duration of tocilizumab treatment, respectively.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			followup time of this cohort since diagnosis was 27 months (range 16-60 months). The patients were treated with TCZ for a mean period of 7.8 months (range 4-12 months). Before TCZ therapy, the patients experienced an average of 2.4 flares/year. All patients entered and maintained clinical remission during TCZ therapy. The mean daily prednisone dosages before and after TCZ initiation were 20.8 mg/day (range 7-34.3 mg/day) and 4.1 mg/day (range 0-10.7 mg/day), respectively (P = 0.0001). The mean erythrocyte sedimentation rate declined from 41.5 mm/hour (range 11-68 mm/hour) to 7 mm/hour (range 2.2-11.3 mm/hour; P = 0.0001)."	
25	Patient/ professional	Polymyalgia Rheumatica & Giant Cell Arteritis UK	In the consultation document, the committee emphasises several times the age demographic of the population with GCA. A misleading impression is given that 'most people with GCA' are in their 80s, although the average age of onset is given as 73. This is illogical, and fails to recognise that there are many people with GCA in their 60s and even in their 50s. When referring to the likelihood of co-morbidities, our representative did mention that many people with GCA are elderly, but certainly did not say that 'most people are in their 80s". We therefore consider that the assumptions of the committee regarding age range and the calculations regarding QALYs may be skewed and request that these figures are revisited.	Comment noted. The committee recognised that giant cell arteritis is common in people in their 50s and 60s (FAD, section 3.1) but agreed that the mean age (73 years) used in the model is representative of people with this condition in England.
26	Patient/ professional	Polymyalgia Rheumatica & Giant Cell Arteritis UK	Subsequent to the point made above, it is also important to note that in August 2016, NICE published its policy on the use of tocilizumab to treat Takiyasu Arteritis, https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/08/clinical-com-pol-16056p.pdf. A close reading of this document reveals the extent to which Giant Cell Arteritis and Takiyasu's Arteritis are similar, with the exception that TA attacks a younger age group. We note that before the approval of TCZ for Takiyasu's, there was the possibility of treating refractory GCA with other immunosuppressants. However, TCZ was approved for TA, citing evidence from previous studies which included patients with GCA. We quote from page 10 of NICE's clinical commissioning policy on TCZ for TA: The highest level evidence for clinical effectiveness of tocilizumab was from a systematic review and meta-analysis by Osman et al (2014) investigating the role of biological agents in the management of large vessel vasculitis. Out of a total of 25 studies shortlisted, 5 case series with 19 total GCA patients and 4 case series with a total of 11 TAK patients were specific to tocilizumab. There were only 3 RCTs and none of which involved tocilizumab. In the meta-analysis, all 19 GCA patients treated with tocilizumab achieved disease remission. There was CS dose reduction for all patients and total discontinuation of steroids in 9 (47%) patients. Pooled mean CS dose reduction was 16.55 mg per day (95% CI -26.24 to -6.86). As the national (UK-wide) patient organisation representing GCA patients in England, we respectfully request the committee to consider this apparent anomaly of a drug being	Comment noted and was discussed by the Appraisal Committee. The committee explained that giant cell arteritis and Takiyasu's arteritis are two different conditions with different clinical features and treatment requirements. However, please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).

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			approved for one set of patients and failing to be approved for another set of patients with a very similar disease (both forms of large vessel vasculitis, both characterised by over-production of IL-6). This even though the evidence cited in the TA commissioning policy cites evidence about the efficacy of TCZ for GCA. We do suggest that there may be an equality issue for the committee to consider here.	
27	Patient/ professional	Polymyalgia Rheumatica & Giant Cell Arteritis UK	Our final point is that the committee document states that there has been no adequate new treatment for GCA for 'several years'. The fact is that prednisolone was first approved for clinical use in 1955. There has been no significant advance in treatment of GCA for over 60 years, which is longer than the lifetime of some of our members.	Comment noted. The committee recognised that there has been no significant advance in treatment of giant cell arteritis for over 60 years. Please also note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
28	Patient/ professional	Vasculitis UK	I attended the initial STA meeting in November as a Patient Expert and was disappointed with the evidence submitted by the manufacturer and felt the clinical and subjective patient evidence lacked strength. Since the STA I have been seriously ill, so personally unable to coordinate a submission on behalf of Vasculitis UK to this second review meeting. I don't want to waste Committee members' time with unnecessary verbiage. I have no original or new data to contribute. However I have studied the BSR's well substantiated and detailed technical submission and Professor Ann Morgan's excellent submission, made from the viewpoint of a clinician with extensive experience in treating GCA.	Comment noted and thank you for your response.
29	Patient/ professional	Vasculitis UK	Glucocorticoid toxicity has been long recognised as *the* major hazard in the treatment of all types of vasculitis and in recent years has been well addressed in small/medium vessel vasculitis through the use of steroid-sparing immune supressing medication, which permits reduction of glucocorticoids to low levels. However, adjunctive use of these immune suppressing drugs has proved to be largely ineffective in large vessel vasculitis. Thus there is a serious need for a suitable new drug and Tocilizumab *seems* to fit that need.	Comment noted. The committee recognised the high unmet clinical need of people with giant cell arteritis and the seriousness of glucocorticoid-related adverse events/toxicity. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
30	Patient/ professional	Vasculitis UK	We (Vasculitis UK) do recognise that whilst the evidence for routine use of Tocilizumab in GCA may be still lacking in strength of evidence and that, as presented at the STA meeting, the cost is high. However, there is a strong case for use of Tocilizumab in refractory cases, those who have experienced serious side-effects of long term high dose glucocorticoids and those who have been subjected to excessive cumulative dosage of GCs. The BSR offers very good evidence of cost effectiveness in terms of potential cost savings.	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
31	Patient/ professional	Vasculitis UK	Professor Morgan has highlighted the work of the new TARGET partnership and the accumulating data available through the UKIVAS partnership and other sources and the development of new algorithms. She raised the interesting concept of a future	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis

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			collaborative relationship between clinicians, researchers and NICE with a view to ensuring that NICE has early access to the data it needs for its decisions. Thus, realistically and at present, we at Vasculitis UK would be happy were NICE to approve the use of Tocilizumab in selected sub-groups where it is going to be cost effective, of great clinical benefit and with substantial QoL benefit for patients. By the time of the customary review, in two years, there should be an ample body of new and better evidence to consider extending this use.	in adults (FAD, section 1.1).
32	Patient/ professional	British Society for Rheumatology	**Has all of the relevant evidence been taken into account?** The BSR would argue no. In the final recommendations, no clear distinction has been made between the different subsets of GCA. This is despite the consultation document referring to this accepted clinical delineation further on. It is widely accepted that GCA has different subsets; those with purely cranial disease, those with more widespread vascular involvement termed Large Vessel-GCA (LV-GCA), and those with glucocorticoid (GC) refractory and relapsing disease. It is these last 2 groups as well as in patients with co-morbidities or pre-existing adverse effects that may be exacerbated by GC, who are in desperate need of additional treatment options, who need to be considered for Tocilizumab treatment rather than the GCA cohort as a whole. The NICE consultation does not appreciate that the cumulative GC use in these subsets is greatly increased, resulting in significant clinical and economic burden.	Comment noted. Please see section 3.2 of the final appraisal determination (FAD) for the committee's full considerations about subgroups. In addition, please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
33	Patient/ professional	British Society for Rheumatology	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries do not consider the fact that, as with other inflammatory conditions where biologic agents are used, GCA exhibits a range of severity and disease extent. Severe and extensive GCA is unresponsive to GC unless they are maintained long term at doses associated with major toxicity. Severe and extensive GCA is also associated with a higher likelihood of ischaemic complications, vascular damage, including aortic dilatation, and cardiovascular events. Costs averted with efficacious therapy with Tocilizumab in this sub group are the costs of treating serious GC toxicity, vascular damage, cardiovascular and cerebrovascular events **(see review below for details)**. In this sub group of relapsing/refractory patients the cost-effectiveness estimate of Tocilizumab therefore may be much lower. The summaries also assume that GC are tapered in all cases of GCA to zero. This is not the normal rheumatological practice in treatment of other vasculitides and connective tissue diseases where patients are often maintained on low dose GC (< 5 mg daily) along with adjunctive conventional or biologic disease-modifying anti-Rheumatic Drug (c or bDMARD) therapy. Using this model patients with GCA may not require Tocilizumab treatment for greater than 12 months again significantly reducing the cost effectiveness estimate (for details see below). There are no cDMARDS with high quality evidence for	Comment noted. The committee recognised the seriousness of glucocorticoid-related AEs/toxicity and that the subgroup with the highest unmet need is people with relapsing or refractory giant cell arteritis (FAD, section 3.2). Please note that tocilizumab is now recommended as a treatment option for people with relapsed or refractory giant cell arteritis (FAD, section 1.1). Please see sections 3.5 and 3.9 of the final appraisal document (FAD) for the committee's full considerations about steroid taper regimen and duration of tocilizumab treatment, respectively.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			efficacy in GCA.	
34	Patient/ professional	British Society for Rheumatology	**Are the recommendations a sound and suitable basis for guidance to the NHS?** The BSR would argue no. Tapering GC alone may be acceptable for some patients, this is not disputed. However, for LV-GCA and relapsing groups, who by very definition are refractory to GC, there is no proven role for cDMARDs as steroid sparing agents. By not recommending Tocilizumab for these difficult to treat subsets, NICE still leaves an unmet need for efficacious treatment. For these patients, there are no current effective therapies available.	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
35	Patient/ professional	British Society for Rheumatology	**Are there any aspects of the recommendations that need consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** These recommendations may be construed to discriminate against older people and against people who currently have no choice but to take long term steroids for disease control. GCA is a disease of older people, typically affecting people from the age of 50 with a peak incidence some decades later. This is the only vasculitis that is almost exclusively treated with GC monotherapy, due to a lack of treatment alternatives. Age is almost certainly a factor in the historical paucity of clinical trials and high quality clinical data, yet older patients are in the greatest need of GC-sparing medications due to the high GC doses required and higher number of co-morbidities. For patients with osteoporosis, congestive cardiac failure and type II diabetes – the commencement of high-dose prednisolone always means worsening of their other co-morbidity. These patients have no other treatment options. As such, limiting treatment options could be seen to discriminate based on age. Additionally, although GCA predominantly affects older people, many patients with LV-GCA are younger and may still have over a decade left of their working life. Not giving these patients a reasonable treatment alternative is condemning them to a lifetime of significant disability and early unemployment. As we have previously alluded to and explain in more detail in our attached review, those with LV-GCA and GC refractory and relapsing disease are more likely to have increased cumulative GC burden and uncontrolled vascular inflammation. High GC use results in significant disability and co-morbidity, including obesity, diabetes, hypertension, cardiovascular and cerebrovascular events, osteoporosis and fracture, sarcopenia, peptic ulcer disease, ophthalmic complications, adrenal insufficiency and death. Uncontrolled inflammation also increased the risk of direct vascular complications such as aortic aneurysm, dissection and rupture, vascular stenosis, heart failure, valvular regurgitation, peripheral vascular disease, sight loss and cerebrovascular events. These are not only	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1). The committee concluded that its recommendations do not have a different impact on people protected by equality legislation than on the wider population (FAD, section 3.18)

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			expensive to treat, but have significant adverse effects on quality of life and independence.	
36	Patient/ professional	British Society for Rheumatology	**Further comments and rebuttal** (Comments specifically on paragraphs 1.2, 3.1, 3.5 and 3.7).	Thank you for your response. Please see the responses to each comment below.
37	Patient/ professional	British Society for Rheumatology	1.2 The health economic assessment assumed that Tocilizumab would be used for 2 years and concludes that for the average patient with GCA this fails to meet the NICE QALY threshold. The disutility of GCs in the company model was mainly driven by risks of diabetes and fracture. This is an average across the entire population of GCA. For high-risk subgroups (e.g. those who have already had relapses and fragility fractures while on GCs) the disutility of GC therapy is far higher as has been clearly outlined in the above review. This has not been incorporated into the model.	Comment noted. The committee discussed a 1 year stopping rule and concluded that it was appropriate (FAD, section 3.9). The committee considered that the model adequately captures the effects of glucocorticoids on quality of life (FAD, section 3.13)
38	Patient/ professional	British Society for Rheumatology	3.1 The interpretation of the clinical experts' advice is that it is difficult to identify at disease presentation which patients are going to relapse or not. While this may be true, relapsing GCA is a recognised clinical subset and there is general agreement on its features. It is an error of logic to say that because patients with relapsing GCA cannot be reliably identified at disease onset at the group level, they cannot be identified on follow-up. Surely an individual patient with relapsing GCA can be identified reliably by the fact that they have GCA and have had relapses. This is the subgroup with the greatest GC burden, greatest cumulative risk of GC-related complications and probability of vascular damage. It is easy to identify (as outlined above) this subset that would benefit most from Tocilizumab. This group of patients should not be disadvantaged because less severe and less extensive GCA can be managed with lower GC-related toxicity, particularly when no treatment alternatives currently exist.	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
39	Patient/ professional	British Society for Rheumatology	3.5 The 52-week taper recommended by BSR guidelines is a starting-point for clinicians to work from, rather than a description of what actually happens. The guidelines also state that if patients relapse during taper then the dose of GC escalates and this necessarily lengthens the total duration of GC therapy. The reason why GC are tapered over 18-24 months in clinical practice is because patients often relapse during taper. The trial protocol was designed to reflect this practice – with a starting-point of a 52-week taper, but with GC dose escalated in the event of relapse. This was indeed observed in the GiACTA placebo arm in which the GC dose was escalated in many patients due to relapse. Therefore, we would argue that the "52-week taper placebo arm" is not really just 52 weeks of GC and does indeed represent current clinical practice in England. We feel it is an appropriate comparator and it does not bias the results of the trial.	The committee concluded that the 52-week glucocorticoid taper does not reflect clinical practice in England following advice from clinical experts (FAD, section 3.5). However, this tapering regimen and its associated uncertainty was accepted in the cost-effectiveness model (FAD, section 3.15 and 3.16)
40	Patient/ professional	British Society for Rheumatology	3.7 The reason the trial did not show a difference in the rate of GC related adverse events (GC-AE) was that as an efficacy trial it was not powered to show a difference in such rates. Therefore, absence of evidence of a reduction of GC-AE cannot be taken as evidence that Tocilizumab does not reduce the risk of GC-AE. It is far more likely that	Comment noted. Please see section 3.7 of the final appraisal document (FAD) for the committee's full considerations about glucocorticoid-related adverse events.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			because GC-AE are known to relate strongly to cumulative GC dose, the reduction in cumulative GC doses observed in the Tocilizumab arms of the trial is likely to translate to lower long-term risk of GC-AE in GCA patients treated with Tocilizumab.	
41	Patient/ professional	British Society for Rheumatology	**Proposal:** We suggest that based on the literature review and results of trials of Tocilizumab in GCA, including GiACTA, that Tocilizumab has a major role in efficacious and safe management of severe, relapsing and refractory GCA, particularly in those with extensive disease such as LV-GCA, or those with direct vascular complications of uncontrolled disease. Relapsing or refractory disease is defined as relapse on doses >5mg prednisolone daily despite use of the recommended BSR dose reduction regimen. It also has a major role as outlined in our figure, in patients with co-morbidities that may be exacerbated by long term GC therapy or in the presence of GC related serious adverse effects. We propose that patients in these sub-groups are treated with weekly injections of 162mg Tocilizumab for 12 months along with GC doses tapering to less than 5mg in around 6 months provided disease activity remains controlled. Patients who have severe and/or extensive disease at disease onset (such as those with ischaemic symptoms or features of proven LV-GCA) should also be eligible for Tocilizumab treatment for 12 months. We recommend the tapering regimen should be individualised. Possible scenarios for how this could be achieved are outlined below: In patients without ischaemic symptoms, such as jaw claudication or amaurosis fugax on relapse: Prednisolone 20mg daily for 4 weeks, 17.5mg daily for 4 weeks, 15mg daily for 2 weeks, 12.5mg daily for 2 weeks, 10mg daily for 4 weeks, 7.5mg daily for 4 weeks, 5mg daily for 4 weeks thereafter reducing by 1mg every 2-4 weeks in an attempt to achieve the lowest GC dose while maintaining disease remission. In patients with ischaemic symptoms at relapse, higher starting doses of prednisolone will be required (40-60mg). This treatment regimen would allow an additional 6 months treatment with weekly Tocilizumab monotherapy, while on lowest possible dose of prednisolone, to sustain remission. At 12 months Tocilizumab treatment could be stopped for patients in remission. Thereafter, we would recommend individual treatment decisions are taken by the supervising clinician as to whether GC can be stopped altogether or continued at an acceptable low dose (<5mg prednisolone per day) with or without additional immunosuppression for remission maintenance. The scenario could include provision of a second 3 to 6 months course of Tocilizumab therapy in case of a further relapse.	Thank you for your proposal and this was considered by the committee when reaching its conclusion on the recommendation made in the Final Appraisal Determination (FAD, section 1.1).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Our current position on management of relapsing or refractory GCA requires further evidence base. We recommend a research agenda directed at efficacious and safe treatment of this particularly difficult sub-group, with careful documentation of GC toxicities. This may need to include randomised controlled trials of promising c-DMARDs either to induce or maintain remission in GCA.	

Summary of comments received from members of the public

Theme	NICE Response
There are no other effective treatments available	Comments noted. The committee recognised the limited treatment options for people giant cell arteritis. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
GCA is an extremely debilitating disease that drastically affects QoL	Comments noted. The committee recognised that giant cell arteritis is debilitating disease that can drastically affect quality of life. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
There is an unmet need for people with refractory/relapsing GCA	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
Cost may be a factor but patient perspective is equally important	Comments noted. Patient organisation input was fully considered by the committee and has been documented in sections 3.1 and 3.2 of the Final Appraisal Determination (FAD). In addition, comments received from patients and carers during consultation were presented to the appraisal committee. The slides are included in the committee papers for information.
Older population should not be discriminated and denied a treatment that could potentially improve their QoL	Comment noted. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1). **The committee concluded that its recommendations do not have a different impact on people protected by equality legislation than on the wider population (FAD, section 3.18).**
Disagree with clinical experts that the duration of steroids for uncomplicated GCA is 18-24 months – there is a trend to lower doses and shorter courses as used in the GiACTA protocol	The committee concluded that the 52-week glucocorticoid taper does not reflect clinical practice in England following advice from clinical experts (FAD, section 3.5). However, this tapering regimen and its associated uncertainty was accepted in the cost-effectiveness model (FAD, section 3.15 and 3.16)
The age range assumption is incorrect: many people have GCA as early as in the 50s	Comment noted. The committee acknowledged that many people can have giant cell arteritis, with the disease being most common among people 50 years and older, The final appraisal document (FAD) has therefore been amended to reflect this (section3.1).
Steroids alone is not sufficient in controlling pain and inflammation. Tocilizumab could help reduce the steroid dose and cumulative steroid burden as well as associated AEs and improve patient QoL. In addition, it could help people stop "yo-yoing" on steroid doses and eventually become drug-free	Comment noted. The committee recognised the importance of the steroid-sparing effect of tocilizumab. Please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
Tocilizumab has been recommended for a similar condition, Takiyasu's Arteritis, using evidence from GCA population	Comment noted and was discussed by the Appraisal Committee. The committee explained that giant cell arteritis and Takiyasu's arteritis are two different conditions with different clinical features and

	treatment requirements. However, please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).
Tocilizumab is recommended for treating GCA in the USA and Canada, why not in England?	Tocilizumab is considered by the committee within the context of the NHS in England. However, please note that tocilizumab is now recommended as a treatment option for treating relapsed or refractory giant cell arteritis in adults (FAD, section 1.1).

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

Tocilizumab for treating giant cell arteritis [ID1051]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche Products Limited Hexagon Place 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted], Health Economist, Roche Products Limited

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Executive Summary Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for 'Tocilizumab for treating giant cell arteritis [GCA]'. We are disappointed that the Committee was unable to recommend tocilizumab in the ACD. Nevertheless, we appreciate the Committee's desire to ensure any positive recommendation is rooted in patient need and aligned to clinicians' intended use of tocilizumab in this setting. With that in mind, we sought additional input from UK GCA experts to more specifically understand how tocilizumab might be used in practice and to ensure the clinical validity of our response. There is overwhelming clinical support for making tocilizumab available on the NHS for GCA. We have summarised our response below for ease of reading, and our full analysis follows. If any further information is required, we would be happy to provide it in order to aid the Committee's decision making. We trust that the information provided herein will allow NICE to reconsider its provisional recommendation and allow access to tocilizumab on the NHS. **Has all of the relevant evidence been taken into account?**

A body of literature has been published since our original submission, and we have also identified additional publications to address the Committee's particular concerns. These data are identified in the relevant Comments within this response.

Further, published data has been added to the cost-effectiveness model, as described in Comment 8, to provide additional evidence in the health economic analyses. Additionally, minor errors in the economic model have been corrected.

Therefore, Roche believe there is additional relevant evidence to be taken into account, before the guidance is finalised.

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

In this response we provide further interpretations of the clinical and cost-effectiveness evidence, in consultation with expert clinicians from throughout the UK.

We appreciate that the ACD acknowledges the high unmet need in this population and the clinical benefit of tocilizumab. The key areas where we consider the Committee's interpretation of the evidence need reconsidering are:

- The severity of GCA pathophysiology has not been represented to its full extent in the ACD. This is discussed in Comment 1.
- Tocilizumab would be most valuable for relapsed/refractory patients as they have the highest unmet need. This is addressed in Comment 2.
- The ACD understates the serious consequences of the high cumulative steroid doses currently used to treat GCA patients. The current use of steroids in GCA, and how this impacts patients is described in Comments 3, 4 and 5.

Therefore, Roche believe the summaries of clinical and cost effectiveness included in the ACD need to be re-interpreted in light of the above additional evidence.

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

The benefits of tocilizumab in limiting exposure to steroids have not been fully considered in the ACD, particularly for the relapsed/refractory patient population.

Reduction in cumulative steroid burden is a valid and clinically significant treatment goal, as discussed in Comment 3. There is robust clinical evidence for the beneficial impact of tocilizumab on cumulative steroid burden, as demonstrated in the GiACTA study, which is extrapolated to show benefit for long-term steroid-related AEs. This is further elucidated in Comment 6 of this document.

The clinical experts we consulted do not agree with the Committee that long-term use of tocilizumab would be required to achieve clinical benefit for all patients. Conversely, we consider that 12 months of tocilizumab would provide clinically meaningful benefit to patients and be a cost-effective use of NHS resources. Comment 7 describes the rationale for this position.

On the basis of the data and interpretations above, the cost-effectiveness model has been amended, as described in Comment 8. The updated deterministic ICER is £18,898/QALY, clearly demonstrating that 12 months of tocilizumab to treat relapsed/refractory GCA patients is a cost-effective use of NHS resources

Comments below:

1. GCA pathophysiology: the burden on patients and the NHS
2. Patient sub-populations: identifying the greatest unmet need
3. Treatment goal in GCA: reduction in cumulative steroid burden
4. Current standard of care: steroid tapering regimens in UK clinical practice
5. Steroid-related adverse events: the seriousness is understated
6. Clinical effectiveness of tocilizumab: impact on steroid-related toxicities

	7. Duration of tocilizumab treatment: one year of tocilizumab is efficacious and cost-effective 8. Revision of the cost-effectiveness model
1	**GCA pathophysiology: the burden on patients and the NHS** **1.1 Appraisal reference** In Section 3.1 of the ACD, NICE states: "Giant cell arteritis causes inflammation in the walls of the arteries in the head and neck, and less commonly the aorta (known as large vessel giant cell arteritis). The patient experts explained that this causes symptoms such as headache, jaw pain, fatigue and muscle and joint pains. More serious complications include vision loss and stroke, and it is with visual symptoms that people often first present to health services." **1.2 Key points** • Roche consider that the severity of GCA pathophysiology has not been represented to its full extent in the ACD. We request that this be addressed by the Committee in its reconsideration of the evidence • Vascular inflammation and ischaemia can result in serious clinical sequelae such as vision loss, stroke, aortic aneurysm and dissection, and myocardial infarction • Newly published literature confirms that a wide variety of underlying co-morbidities are more common in patients with GCA than reference populations, including cardiovascular diseases, rheumatologic diseases, osteoporosis, severe infections and diabetes • Hospitalisation rates among GCA patients are significantly increased, compared to matched controls • The above considerations are discussed in relation to the economic model in Comment 8.8 **1.3 Clinical features of GCA** Roche considers that the severity of GCA pathophysiology has not been represented in its full extend in the ACD. GCA is characterised by a wide range of cranial and systemic manifestations including headache, fever and polymyalgia rheumatica. In some cases, a variety of severe ischemic symptoms can occur, of which the most important are ocular manifestations and stroke. Visual impairment and permanent vision loss are particularly dreaded complications of GCA (Dejaco et al. 2017; Kermani et al. 2017; Bukhari 2017; Koster et al. 2018). Additionally, vascular inflammation may lead to large-vessel complications such as arterial stenosis, vascular occlusion, myocardial infarction, aortic aneurysm, aortic dissection and upper limb ischaemia (Dejaco et al. 2017; Mohammad et al. 2017; Kermani et al. 2017; Koster et al. 2018). Clinical experts consulted for this response advise that the current cost to the NHS of managing GCA is high, particularly for those patients with ischaemic and/or large vessel complications. Likewise, the quality-of-life cost for patients and their carers is significant. **1.4 Co-morbidities in GCA** Elderly patients with GCA treated with high doses of corticosteroids are bound to have multiple medical problems. This has been quantified in a population-based cohort study of biopsy-proven GCA patients (Mohammad et al. 2017) which was not incorporated in our original submission. Specifically, they studied the frequency of comorbidities among 768 patients with GCA and compared rates to a reference group of 3,066 reference population patients.

An increased relative risk (RR) of comorbidities was found for:

- Osteoporosis: RR 2.81, 95% CI 2.33–3.37
- Venous thromboembolic diseases: RR 2.36, 95% CI 1.61–3.40
- Severe infections: RR 1.85, 95% CI 1.57–2.18
- Thyroid diseases: RR 1.55, 95% CI 1.25–1.91
- Cerebrovascular accidents: RR 1.40, 95% CI 1.12–1.74
- Diabetes mellitus: RR 1.29, 95% CI 1.05–1.56
- Ischemic heart disease: RR 1.20, 95% CI 1.00–1.44; NS

These results are similar to those of previously reported increased rates of stroke, myocardial infarction, and peripheral vascular disease among patients with GCA in a large UK-based population (Petri et al. 2015).

The comorbidities associated with GCA versus matched patients receiving steroid treatment were summarised following an extensive analysis of the UKs primary research database, the Clinical Practice Research Database (Table 1).

Table 1: Comorbidities associated with GCA versus matched patients receiving steroid treatment (Wilson et al. 2017)

Characteristics	GCA group, $n = 5011$	Non-GCA group, $n = 5011$	χ^2
Comorbidity			
Rheumatologic disease	1090 (21.8)	274 (5.5)	< **0.0001**
Polymyalgia rheumatica	911 (18.2)	127 (2.5)	< **0.0001**
Renal disease	446 (8.9)	358 (7.1)	**0.0012**
Peripheral vascular disease	296 (5.9)	224 (4.5)	**0.0012**
Peptic ulcer disease	299 (6.0)	245 (4.9)	**0.0173**
Myocardial infarction	305 (6.1)	255 (5.1)	**0.0297**
Mild liver disease	1 (0.02)	2 (0.04)	0.5636
Moderate liver disease	32 (0.64)	12 (0.24)	**0.0025**
Hemiplegia	25 (0.5)	21 (0.4)	0.5544
Diabetes	516 (10.3)	484 (9.7)	0.2862
Diabetes with complications	119 (2.4)	105 (2.1)	0.3441
Dementia	32 (0.6)	58 (1.4)	**0.0003**
Congestive heart disease	300 (6.0)	228 (4.6)	**0.0013**
Chronic pulmonary disease	1249 (24.9)	952 (19.0)	< **0.0001**
Cerebrovascular disease	521 (10.4)	376 (7.5)	< **0.0001**
Average number comorbidities	1.03	0.70	–

1.5 Hospitalisation rates

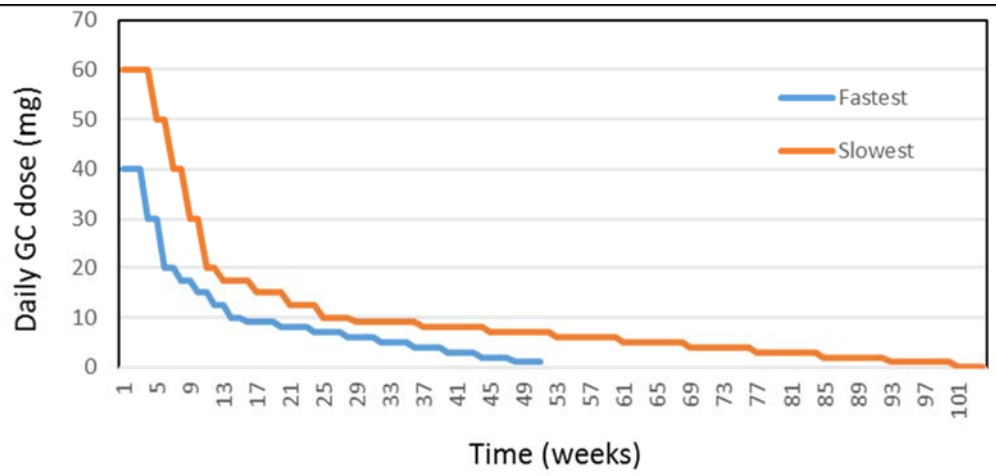
The 2017 CPRD analysis (Wilson et al. 2017a) reported that the hospitalisation rate among GCA patients was significantly increased, compared to matched controls (Incidence Rate Ratio of 1.7, with 95% confidence interval of 1.6 - 1.8).

The most common causes of hospitalisation in the GCA group were diseases of the cardiovascular system, closely followed by diseases of the digestive system and of the eyes. It appears likely that this observation reflects both steroid-related AEs and the pathophysiology of GCA, in which

	increased risks for cardiovascular disease and vision impairment have been observed independently of glucocorticoid use. **1.6 Summary** Roche considers that the severity of GCA pathophysiology has not been represented to its full extent in the ACD. The management of large-vessel and ischaemic complications of GCA, in particular, are costly and resource heavy. This position is supported by newly published literature and expert clinical opinion. Consequently, the current burden on patients, their carers and NHS resources is not comprehensively described in the ACD. This therefore diminishes the positive benefits that tocilizumab can provide. We request that this be addressed by the Committee in its reconsideration of the evidence. Further amendments to the cost-effectiveness model have been made to incorporate more granular disease management costs (see Comment 8).
2	**Patient sub-populations: identifying the greatest unmet need** **2.1** Appraisal reference In Section 3.2 of the ACD, NICE states: "People with relapsing disease are usually offered lower doses of corticosteroids in an attempt to manage flares and minimise additional steroid exposure; as such, the clinical experts considered that tocilizumab would be most valuable to people with relapsing disease." **2.2 Key points** • Patients with relapsed or refractory GCA have the highest unmet need • Other subgroups are not able to be robustly analysed with current evidence • The amended cost-effectiveness model in Comment 8 is targeted to relapse/refractory GCA patients **2.3 Relapsed and refractory patients** Roche agrees with the Committee that tocilizumab would be most valuable for patients with relapsing or refractory GCA. However, we consider that the rationale for this has not been fully elucidated in the ACD. Primarily, relapsed/refractory patients are likely to have: (Stone et al. 2017; Wilson et al. 2017; Research Partnerships 2017) • sub-optimally treated disease, by definition • pre-existing high cumulative steroid burden • greater concomitant medication usage • higher body weight • greater burden of comorbidities This position is supported by the expert clinicians and patient organisations consulted by NICE in advance of the Appraisal Committee Meeting (https://www.nice.org.uk/guidance/gid-ta10172/documents/committee-papers). In response to question 11 of the consultation, the patient organisation PMRGCA stated: "People who might benefit more [from tocilizumab]: a) People with pre-existing conditions such as diabetes, hypertension, for whom long-term glucocorticosteroids are contra-indicated

	b) People who have exhibited an intolerance to steroids, such as steroid psychosis. c) People who are at work, or who have significant caring responsibilities or other factors making it more likely that they will experience 'flares' or relapses d) People with an existing history of relapse or flare, requiring them to increase their dose of GCs back up to the level of a previous dose." In response to question 12 of the consultation, the BSR stated: "All patients with relapsing disease and disease refractory to >15mg prednisolone/day will be greatly benefited from this drug. Those with steroid psychosis, congestive cardiac failure, brittle diabetes etc (contraindications to high dose prednisolone therapy) will benefit greatly." Further, subgroup analysis was previously provided for the relapsed/refractory population, which was discussed in the Appraisal Committee Meeting, but was not reported in the ACD. **2.4 Other potential subgroups** Roche agrees with the Committee that there may be other relevant subgroups of patients with GCA, as described in Section 3.2 of the ACD, for example large-vessel GCA. Roche considers that there is also clinical plausibility for a subset of patients with newly-diagnosed GCA for whom tocilizumab would be valuable. Specifically, those who cannot tolerate glucocorticoids and those who are at high risk for steroid-related AEs (Bukhari M, 2017). For example, patients with pre-existing: • high cardiovascular risk • osteoporosis or osteopenia • obesity • diabetes However, robust evidence demonstrating efficacy in these sub-groups is lacking, due to small patient numbers. We have concerns about the interpretation of any such analyses as they would not be sufficiently powered to report any meaningful differences. **2.5 Summary** Roche agrees that the relapsed/refractory patient population would derive the most benefit from treatment with tocilizumab and would be the most responsible use of NHS resources. This position is supported by recently-published literature and the opinions of clinical experts and patient organisations. Likewise, this is the preferred assumption of the NICE ERG. Therefore, our revised economic model, described in Comment 8, reports the cost-effectiveness of tocilizumab for only patients with relapsed/refractory disease.
3	**Treatment goal in GCA: reduction in cumulative steroid burden** **3.1 Appraisal reference** In Section 3.1 of the ACD, NICE states: "People would welcome a new treatment that reduces the cumulative amount of steroids needed." **3.2 Key points** • Roche agrees that reduction in cumulative steroid burden is a valid and clinically significant treatment goal • UK clinical experts treating GCA consulted for this ACD response support this • However, this has not been reflected in subsequent parts of the ACD and therefore, Roche requests that this be addressed by the Committee in its reconsideration of the evidence

	3.3 Discussion Roche and clinical experts agree that reduction in cumulative steroid burden is a legitimate and important clinical aim in GCA. This is elucidated further below (Comments 4 and 5) and underscores the substantial unmet need for alternative treatment options for GCA. This aim validates the important steroid-sparing effect of tocilizumab in GCA patients, as demonstrated in the GiACTA study. Therefore, Roche considers that this highlights the urgency of making tocilizumab available to GCA patients in the UK. We request that this treatment goal be clearly reflected in the Committee's reconsideration.
4	**Current standard of care: steroid tapering regimens** **4.1 Appraisal reference** In Section 3.5 of the ACD, NICE states: "The committee was concerned that 52 weeks (12 months) is the minimum steroid taper recommended in the British Society for Rheumatology guidelines. The clinical experts explained that in clinical practice, corticosteroids would usually be tapered over 18 to 24 months. The committee considered that this might mean that the number of flares in the comparator arm (that is, placebo with 52-week steroid taper) may be higher, and the time to first flare shorter, than in clinical practice in England. The committee was also aware that 49% of patients in the comparator arm did not have disease remission after the 6 week screening phase of the trial, but that nonetheless they had to start the 52-week tapering regimen. The committee was concerned that this might bias the primary end point of the trial (sustained remission at 52 weeks) in favour of tocilizumab, because it is less likely that people whose disease has not responded to high-dose steroids would achieve remission with lower doses. The committee concluded that the 52-week steroid taper arm of the trial does not reflect clinical practice in England and might bias the results in favour of tocilizumab." **4.2 Key points** • Roche and clinical experts agree that tapering steroids over 52 weeks, as the 'fastest' BSR recommended regimen, may not reflect current real world clinical practice in the NHS • We have addressed this in the updated cost-effectiveness calculations, see Comment 8.4. **4.3 UK clinical guidelines** The BSR Guidelines (2010) suggest the following tapering regimen (assuming no GCA relapse): • 40–60mg prednisolone continued until symptoms and laboratory abnormalities resolve (at least 3–4 weeks); • then dose is reduced by 10mg every 2 weeks to 20 mg; • then by 2.5mg every 2–4 weeks to 10 mg; and • then by 1mg every 1–2 months provided there is no relapse. For illustrative purposes, Roche has mapped what the 'fastest' possible and 'slowest' possible BSR tapering regimens look like (Figure 1). **Figure 1: BSR treatment guidelines for GCA patients give a range of glucocorticoid tapering regimens**



This tapering is often not straightforward (Mukhtyar et al. 2009). A large proportion of patients (30-50%, Muratore et al. 2013) will experience relapse or flare upon steroid taper, most within the first few months after diagnosis and usually at a daily dose of 5-10 mg (Chandran et al. 2015). This necessitates a further increase in steroid dose to regain disease control. Cessation of steroids may take up to two years.

4.4 Clinical opinion

Roche has consulted clinical experts to clarify the most common steroid taper regimen in current UK clinical practice. They advised that, although the 52-week taper is recommended in the guidelines, this is often not achievable in real world clinical practice. Many patients relapse during the taper and require an increase in dose, which inevitably extends the overall taper period.

For patients treated with tocilizumab, clinical experts have expressed support for the 26-week steroid tapering regimen, in alignment with the results of the GiACTA trial.

4.5 GiACTA baseline remission status

Although 49% of patients in the comparator arm were not in disease remission after the 6 week screening phase, a new exploratory analysis showed no difference in primary endpoint when analysed by remission status at baseline (Table 2).

Table 2:Exploratory analysis of primary endpoint analysed by remission status

	Sustained remission at week 52	
	Remission at BL	No Remission at BL
PBO+52	19.2%	16.0%
TCZ QW	60.0%	52.3%
Delta (TCZ – PBO)	40.8	36.3

Source: Stone et al. 2017

4.6 Summary

Roche and clinical experts agree with the Committee that tapering steroids over 52 weeks is the fastest recommended regimen, and may not reflect real world clinical practice in the NHS.

Therefore, we have revised the prednisone-only arm of the cost-effectiveness model, to incorporate the slowest steroid taper regimen recommended by the BSR Guidelines.

Tocilizumab for treating giant cell arteritis [ID1051]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

5	**Steroid-related adverse events: the seriousness is understated** **5.1 Appraisal reference** In Section 1 of the ACD, NICE states: "Giant cell arteritis is usually treated with a high dose of corticosteroids, which is gradually reduced over time. High doses of corticosteroids may cause skin problems and weight gain, and long-term use can lead to diabetes and osteoporosis." **5.2 Key points** • Roche considers that the ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients. We request that this be addressed in the Committee's reconsideration of tocilizumab • The seriousness of steroid-related AEs has been clearly described in the literature, including recently-published reviews of the evidence in GCA patients • There are clear correlations between increasing harm and increasing average daily dose, as well as increasing cumulative steroid dose • The EULAR taskforce recommends that at ≤5 mg/day steroids there is an acceptably low level of harm • To more accurately represent this position, more granularity has been applied to the cost-effectiveness model, as described in Comment 8 **5.3 Seriousness of steroid-related adverse effects** While Roche appreciates that steroids are the current mainstay of treatment for patients with GCA, steroid-related AEs and morbidity are common and potentially serious. The seriousness of these AEs has been clearly reiterated in multiple recently-published and in-press reviews of the evidence which have not previously been taken into account by NICE (Dejaco et al. 2017; Kermani et al. 2017; Bukhari 2017; ; [redacted] Kermani et al. (2017) undertook a longitudinal study to assess damage in patients with GCA. After a median observation of 3.5 years, >80% of patients with GCA had at least one item of damage. New items of damage were observed in more than half of the patients in this cohort, with the majority being related to treatment. They conclude that "Better therapeutics for GCA that target disease activity and reduce the cumulative burden of disease- and treatment-associated damage are needed." [redacted] [redacted] Other published evidence shows 86% of GCA patients experience steroid-related AEs after 10 years of follow-up. Serious AEs include bone fractures, hip necrosis, diabetes, infections, gastrointestinal

bleeding, cataracts, hypertension, skin-thinning and hirsutism (Nesher, Sonnenblick, and Friedlander 1994; Proven et al. 2003; Petri et al. 2015; Broder et al. 2016).

For the purposes of this response, Roche sought additional data specific to steroid-related AEs.

In 2011, Sarnes et al. published a systematic review of the incidences of and risks for AEs associated with oral and parenteral corticosteroids in the general US population (Table 3). Forty-seven studies were included.

Across patient populations, the most frequently reported corticosteroid-associated AEs were psychiatric events, infections, gastric conditions, and fractures.

Corticosteroid-associated AEs reported to occur at an incidence >30% were sleep disturbances, lipodystrophy, adrenal suppression, metabolic syndrome, weight gain, and hypertension. Vertebral fractures were reported at an incidence of 21% to 30%.

Table 3 shows the AEs categorised by risk measure (including hazard ratios, incidence risk ratios, relative risks, and odds ratios) across patient populations. The time frames over which risks were characterised varied among studies. Only AEs with a significant difference between patients who received corticosteroids and those who did not receive corticosteroids are listed. AEs having a strong association with corticosteroid therapy were fractures, cardiovascular disorders and events, gastrointestinal disorders and events, and infections.

Table 3: GC-related AEs reported in the literature, including the highest reported risk ratio

Steroid-related AEs in any population	Highest reported risk ratio
Any fracture	3 - <5
Back pain	1 - <2
Bacterial sepsis	1 - <2
Basal cell carcinoma	1 - <2
Bladder cancer	2 - <3
Bleeding	1 - <2
Bruising	≥5
Cataracts	≥5
Cushingoid phenotype†	≥5
Diabetes	1 - <2
Ecchymosis	≥5
Epistaxis	≥5
Gastric damage	2 - <3
Gastric lesions/ulcer‡	≥5
GI hemorrhage	1 - <2
Height loss of 2.5 cm	1 - <2
Hip/femur fracture§	≥5
Hospitalization for atrial fibrillation or flutter	≥5
Hypertension	2 - <3
Hypokalemia	1 - <2
Infection	2 - <3
Leg edema	2 - <3
Lethal infection	≥5
Mental status change	≥5
Muscle weakness	≥5
Myocardial infarction	2 - <3
Non-Hodgkin's lymphoma	2 - <3
Nonlethal infections	2 - <3
Oral candidiasis	≥5
Osteonecrosis of femoral head¶	≥5
Parchmentlike skin	3 - <5

Peptic ulcer‡	1 - <2
Ribs/sternum fracture	3 - <5
Sleep disturbance	1 - <2
Squamous cell carcinoma	≥5
Tuberculosis#	≥5
Ulcers	3 - <5
Upper GI complications	1 - <2
Upper limb fracture (not wrist)	2 - <3
Varicella infection	≥5
Vertebral fracture§	≥5
Weight gain	2 - <3

GI: gastrointestinal. *Only AEs with a statistically significant difference in risk between patients receiving corticosteroids and those not receiving corticosteroids are listed. Some studies may have been underpowered to detect significant differences. The risk ratio could reflect a hazard ratio, an incidence risk ratio, a relative risk, or an odds ratio. † Risk for Cushingoid phenotype increased with higher corticosteroid dose. ‡ Risk for gastrointestinal ulcers/lesions varied by study and appeared to increase with higher corticosteroid dose. § Risk for vertebral fracture and hip/femur fracture increased with higher corticosteroid dose and in certain patient populations (e.g. the elderly). Risk for infection varied by type of infection and by study. Risk for osteonecrosis of the femoral head varied by study and patient population. # Risk for tuberculosis varied by study.
Source: Sarnes et al. 2011

5.4 Impact of steroids on GCA patients' quality of life

Research by the GCA and PMR Charity Group, PMRGCAUK, found "coming off steroids" and "living with steroids" are highly important to individuals with GCA (www.pmrgca.co.uk).

Steroid-related AEs are likely to be exacerbated in the GCA population who are predominantly females over 50 years old. They are likely to be suffering from pre-existing multiple co-morbidities which may pose relative or absolute contraindications to steroid therapy (Dejaco et al. 2017).

5.5 Assessing harm associated with steroid dose

The level of harm associated with steroid therapy depends on mean daily dose, total duration of intake and cumulative dose (Strehl et al. 2016; Harris et al. 2015; [redacted]

Broder et al. (2016) have shown in a recent retrospective study, that for each 1,000 mg increase in cumulative glucocorticoid dose, the hazard ratio for AEs is increased by 3%.

Wilson et al. 2017 provides robust evidence of the link between steroid dose and serious AEs. They described serious AEs associated with steroid therapy in patients with GCA in a nested case-control analysis from a large (n=5011) UK CPRD database. The majority of cases of diabetes, glaucoma, and osteoporosis occurred within 2 years following steroid treatment initiation, with over 40% of diabetes and glaucoma cases developing in the first year.

There was a clear trend of increasing risk with increasing average daily dose; GCA patients exposed to higher average daily prednisolone dose were at significantly increased risk of developing diabetes, glaucoma, osteoporosis, fractures, serious infections, and death compared to those with lower doses (Table 4).

Hence, tocilizumab can be expected to bring clinical benefit to GCA patients, even over a period of time shorter than the length of active disease.

Table 4: Adjusted odds ratios for outcomes of interest according to average daily prednisolone dose in GCA patients

	Fractures			Osteoporosis			Infection			Death		
Average daily prednisolone dose (mg/d)[a]	Cases $n = 408$ (%)	Controls $n = 1586$ (%)	AOR (95% CI)[b]	Cases $n = 511$ (%)	Controls $n = 1821$ (%)	AOR (95% CI)[c]	Cases $n = 433$ (%)	Controls $n = 1421$ (%)	AOR (95% CI)[d]	Cases $n = 517$ (%)	Controls $n = 1774$ (%)	AOR (95% CI)[e]
≤5	88 (21.6)	409 (25.8)	1.00	79 (15.5)	391 (21.5)	1.00	76 (17.6)	310 (21.8)	1.00	113 (21.9)	478 (26.9)	1.00
>5 to ≤10	128 (31.4)	575 (36.3)	1.1 (0.8–1.5)	177 (34.6)	619 (34.0)	1.3 (1.0–1.8)	136 (31.4)	476 (33.5)	1.1 (0.8–1.6)	197 (38.1)	695 (39.2)	1.1 (0.8–1.5)
>10 to ≤20	119 (29.2)	394 (24.8)	**1.9 (1.3–2.6)**	148 (29.0)	329 (18.1)	**1.5 (1.1–2.2)**	105 (24.2)	390 (27.4)	1.3 (0.9–1.9)	123 (23.8)	374 (21.1)	1.4 (1.0–2.0)
>20 to ≤30	32 (7.8)	105 (6.6)	**2.0 (1.2–3.2)**	150 (29.4)	157 (8.6)	**1.7 (1.1–2.7)**	39 (9.0)	114 (8.0)	1.7 (1.0–2.7)	41 (7.9)	125 (7.0)	1.7 (1.0–2.8)
>30	41 (10.0)	103 (6.5)	**2.6 (1.6–4.3)**	57 (11.2)	172 (9.4)	**1.9 (1.2–2.9)**	77 (17.8)	131 (9.2)	**3.3 (2.2–5.2)**	43 (8.3)	102 (5.7)	**2.1 (1.3–3.5)**
p^{trend}			**<0.001**			**0.0020**			**<.0001**			**<0.001**

Diabetes			Glaucoma		
Cases $n = 321$ (%)	Controls $n = 1272$ (%)	AOR (95% CI)[f]	Cases $n = 243$ (%)	Controls $n = 957$ (%)	AOR (95% CI)[g]
55 (17.1)	280 (22.0)	1.00	39 (16.0)	187 (19.5)	1.00
75 (23.4)	436 (34.3)	0.9 (0.6–1.4)	74 (30.5)	344 (35.9)	1.1 (0.7–1.7)
73 (22.7)	350 (27.5)	1.2 (0.7–1.8)	59 (24.3)	275 (28.7)	1.1 (0.7–1.8)
38 (11.8)	105 (8.3)	**2.5 (1.4–4.3)**	24 (9.9)	76 (7.9)	1.6 (0.9–3.0)
80 (24.9)	101 (7.9)	**4.7 (2.8–7.8)**	47 (19.3)	75 (7.8)	**3.5 (2.0–6.1)**
		<0.001			**<0.001**

Values in bold are statistically significant. CI, confidence interval; AOR, adjusted odds ratio.

[a] The median range for total duration of prednisolone use (days) across all outcomes for cases and controls respectively was 765–1302 and 528–994 for <5 mg, 625–1152 and 656–941 for >5 to ≤10 mg, 347–607 and 364–470 for >10 to ≤20 mg, 109–226 and 112–154 for >20 to ≤30 mg, 43–74 and 20–50 for >30 mg.

[b] Adjusted for smoking status, BMI, osteoporosis, vision disturbances, epilepsy, dyspepsia, dementia, vitamin D supplementation, steroid injection, past prednisolone prescription, and GCA duration.

[c] Adjusted for alcohol status, smoking status, BMI, COPD, past history of fractures, calcium supplementation, immunosuppressant use, and GCA duration.

[d] Adjusted for alcohol status, smoking status, BMI, diabetes, cardiovascular disease, COPD, and GCA disease duration.

[e] Adjusted for alcohol status, smoking status, BMI, COPD, stroke, cardiovascular disease, sepsis, diabetes, pneumonia, ulcer, epilepsy, dementia, thrombocyte aggregation inhibitor use, vitamin K use, proton pump inhibitor use, nitrate use, and GCA duration.

[f] Adjusted for alcohol status, smoking status, BMI, COPD, stroke, bisphosphonate use, coronary vasodilator use, vitamin K use, statin use, and GCA duration.

[g] Adjusted for BMI, ocular steroid use, history of thrombocyte aggregation inhibitors use, beta blocker use, insulin treatment, and GCA duration.

Source: Wilson et al. 2017

With regard to mean daily dose, a 2015 EULAR task force considered that for long-term steroid use (3- 6 months or more): (Strehl et al. 2016)

- At ≤5 mg/day, there is an acceptably low level of harm for the specified outcomes (with the exception of patients at high risk for CVD who may require preventive measures)
- At >10 mg/day, the risk of harm is high
- At dosages between >5 and ≤10 mg/day, uncertainty still exists and, consequently, patient-specific characteristics need particular consideration to interpret and estimate the individual risk of harm

This reiterated in the in-press Buttgereit et al (2018) review of the evidence.

5.6 Steroid doses in GCA

Patients with GCA generally require higher starting doses and longer duration of steroid therapy than patients with other systemic inflammatory diseases [redacted]

Indeed, recent US claims-based data suggest that patients with GCA typically receive cumulative glucocorticoid doses of >5,000 mg prednisone-equivalent over the course of several years (Broder et al. 2016).

A similar large UK database of 3,074 patients with GCA demonstrated that 33% of patients were treated with a cumulative dose of prednisone >10,000 mg (Petri 2015).

Trends in recent decades for steroid use in GCA also suggest increasing cumulative doses and longer exposures (Chandran et al. 2015; [redacted]

Patients with refractory disease are by definition poor responders to steroids, with frequent relapse and flare. As such they require much higher and prolonged courses whilst an effective steroid-sparing agent is sought, with higher cumulative doses. This further validates our position in Comment 2.

5.7 Summary

Roche considers that the ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients. This position is supported by recently published literature and

	expert clinical opinion. Roche requests that this be reflected in the Committee's reconsideration of the evidence. There are clear correlations between increasing harm and increasing average daily steroid dose, as well as increasing cumulative steroid dose. At ≤5 mg/day, there is an acceptably low level of harm. This has been considered further in our economic model in Comment 8. Nevertheless, it is challenging to incorporate many steroid-related AEs into the cost-effectiveness model. On this basis, Roche requests that NICE takes into account that the modelled ICER is likely to be an overestimate.
6	**Clinical effectiveness of tocilizumab: impact on steroid-related toxicities** **6.1 Appraisal reference** In Section 3.7 of the ACD, NICE states: "Because tocilizumab is taken with corticosteroids, the extent to which steroid-related adverse events are reduced is unclear. One of the main perceived benefits of tocilizumab is a reduction in cumulative steroid dose and risk of steroid-related adverse events. The committee noted that although the initial tapering regimen with tocilizumab is shorter than when corticosteroids are used alone, disease flare ups are treated by increasing the steroid dose, and a tapering regimen restarted. As such, people taking tocilizumab could still be exposed to large cumulative doses of corticosteroids. The committee acknowledged that the median cumulative steroid dose was lower in the tocilizumab arm of GiACTA (see table 1), but noted that this was over the relatively short 52-week follow-up. It was concerned that despite the lower median cumulative steroid dose in the tocilizumab arm, the rate of steroid-related adverse events was similar between arms (50% vs. 49%). The committee concluded that because corticosteroids still need to be taken with tocilizumab, the extent to which steroid-related adverse events are reduced is unclear." **6.2 Key points** • Roche considers that there is robust clinical evidence for the impact of tocilizumab on cumulative steroid burden, and therefore steroid-related AEs. We request that this be reflected in the Committee's reconsideration of the evidence. • GiACTA shows that tocilizumab enables a clinically significant >50% reduction in cumulative steroid burden over 52 weeks, achieved through: o more rapid steroid taper o reduction in the rate of flare • Post-hoc analysis has shown that patients on the placebo arms of GiACTA had [redacted] **6.3 Reduction in cumulative steroid burden in GiACTA** Roche agrees with the Committee that one of the main benefits of tocilizumab therapy is the reduction in cumulative steroid dose; this is achieved by both allowing a rapid taper of steroid and by decreasing the flare rate (Stone et al. 2017; Bukhari, M. 2017; [redacted] However, Roche disagrees that the "extent to which steroid-related adverse events are reduced is unclear". Over the 52-week duration of GiACTA there was >50% reduction in cumulative steroid burden for patients taking tocilizumab. • 1,862 mg for tocilizumab + 26-week steroid taper • 3,818 mg for placebo + 52-week steroid taper Given that there is a 3% increase in relative risk of AEs with each gram of cumulative steroid (see Comment 5 above; Broder et al. 2016), the difference seen in GiACTA is highly clinically relevant.

This is especially urgent in the light of the data by Petri et al (2015) showing that over one third of UK GCA patients have been exposed to >10,000 mg of steroids, with all the inherent risks this poses.

6.4 Rapidity of steroid taper

Roche would like point out that many patients on tocilizumab can taper to zero steroid within six months, after which they are managed on tocilizumab monotherapy.

As discussed in Comment 4.5, for patients treated with tocilizumab, clinical experts have expressed support for the 26-week steroid tapering regimen, in alignment with the results of GiACTA.

6.5 Rate of steroid-related AEs in GiACTA

Roche considers that there are valid explanations for the similar rate of steroid-related AEs in the GiACTA arms (50% vs. 49%), despite the lower median cumulative steroid dose in the tocilizumab arm.

Firstly, GiACTA was not designed to fully ascertain the long-term steroid-sparing benefit of tocilizumab, or the safety events related to steroid use, since this would require trials of considerable duration.

Further, it is important to note that many steroid-related AEs manifest in the longer-term, and therefore we would not expect to see significant differences over the course of the 52-week study.

Additionally, the steroid-related AEs reported in our original submitted dossier (Table 5) are (S)AEs considered related to blinded study treatment by the investigator. The investigators made clinical judgements without knowing the arm of the study the patient was in.

Table 5: Adverse events in GiACTA by arm and by investigator judgment of relatedness

Study arm	SAEs at Week 52 (none were fatal) (numerically higher for PBO)	AEs/100 patient years (numerically higher for PBO)	AEs related to blinded treatment	SAEs related to blinded treatment	AEs related to STEROID USE
PBO+26	22%	990.8	64%	14%	62%
PBO+52	25.5%	1011.2	53%	12%	49%
TCZ QW	15%	872.0	68%	6%	50%
TCZ Q2W	14.3%	948.0	74%	4%	61%

To validate these findings, Roche has since undertaken a further analysis of GiACTA to determine which AEs could be considered related to steroid use. These data have not previously been considered by NICE. It is important to note that these data were analysed retrospectively and were not based on standard or pre-specified criteria.

Events that were consistent with steroid-induced toxicity from Part 1 of GiACTA [redacted] These included [redacted]

The results show [redacted] of steroid-induced toxicity events being seen in the placebo + 52 week taper arm and [redacted] being seen in the tocilizumab QW

arm. This post-hoc analysis shows [redacted] (Table 6).

Table 6: Rates of steroid-related toxicity in post-hoc analysis of GiACTA

	Steroid-induced toxicity events
PBO+26	[redacted]
PBO+52	[redacted]
TCZ QW	[redacted]
TCZ Q2W	[redacted]

6.6 Summary

Roche considers that there is robust clinical evidence for the beneficial impact of tocilizumab on cumulative steroid burden, and therefore steroid-related AEs. We request that this be reflected in the Committee's reconsideration of the evidence.

As described in Comment 5, it has been proven that steroids are clearly associated with a range of serious adverse events.

Further, there is a robust body of evidence linking dose and cumulative steroid burden to increased risk of harm, as described in Comment 5. Reduction in cumulative steroid burden is a clinically valid treatment goal, as discussed in Comment 2.

GiACTA showed that tocilizumab reduces the cumulative steroid dose for patients by >50%, as well as reducing the flare rate.

Consequently, it is logical to expect a subsequent reduction in harm and clinically significant benefit for patients taking tocilizumab.

[redacted]

Therefore, we consider that making tocilizumab available on to GCA patients in the UK would be a rational use of NHS resources.

7	**Duration of tocilizumab treatment: 12 months of tocilizumab is efficacious and cost-effective**

7.1 Appraisal reference

In Section 3.9 of the ACD, NICE states: "The company assumed in their economic model that treatment with tocilizumab stops after 2 years. However, the committee was concerned that in clinical practice treatment may continue well beyond 2 years. This is because the risk of relapse continues, and there is no evidence that tocilizumab modifies the underlying disease when treatment stops (it may just supress it for the duration of treatment). The committee was aware that in both the preliminary results of the GiACTA follow-up study and in a smaller phase II study (NCT01450137), around half the patients' disease relapsed after stopping tocilizumab. The clinical experts commented that if the disease was controlled after 2 years of treatment, the interval between treatments could potentially be increased. In addition, tocilizumab treatment may be stopped and only restarted in the event of a relapse."

7.2 Key points

- Roche and clinical experts consider that 12 months tocilizumab treatment would provide clinically relevant efficacy and be a responsible use of NHS resources. We request that the Committee's reconsideration reflects this stance
- GiACTA has shown that 12 months of tocilizumab is highly effective in sustaining remission and reducing cumulative steroid burden
- In a new review of published case series', the majority of patients received tocilizumab for much less than one year (range 1 to 53 months)
- For those patients who are unable to taper to 0 mg steroid in 52 weeks, expert clinicians and international clinical guidelines agree 5-7.5 mg/day to be an acceptable maintenance steroid dose
- Consequently, our revised cost-effectiveness model incorporates 12 months of tocilizumab therapy for relapsed/refractory patients.

7.3 Expert clinical opinion

Upon consultation with expert clinicians, it has become clear that two years of tocilizumab treatment would not be required for the vast majority of patients.

There is broad clinical support for reimbursing 12 months of tocilizumab, as a judicious use of NHS resources.

Indeed, many patients would require less than 12 months of treatment to achieve sustainable remission, although this is difficult to quantify.

7.4 Sustained remission rates after 12 months of tocilizumab

In the GiACTA study, treatment with tocilizumab over 52 weeks was shown to be highly effective in sustaining remission and reducing cumulative steroid burden (Stone et al. 2017).

In the previously provided Part 2 follow-up, although incomplete, [redacted] of patients who had previously been in either of the tocilizumab arms (or [redacted] of those on QW tocilizumab) were still in sustained remission once they had stopped taking study drug and who had reached Study Week 100 or beyond. This highlights that one year of treatment with tocilizumab is sufficient to sustain remission in the longer term and thereby reduces the steroid burden in these patients.

The supporting data from Adler et al. (2016), reported in the our originally submitted dossier, also showed, albeit with very small numbers, that a substantial proportion of patients remained in remission after their last infusion of tocilizumab; 45% had not relapsed after a median follow-up time of 12.5 months.

7.5 Duration of treatment in case series'

Since the Committee meeting, Roche has undertaken a literature review of published case reports of the use of tocilizumab in GCA (undertaken on 23 November 2017; Evans et al., 2016; Loricera et al.; 2015, Regent et al., 2016; Aitisha & Fayad., 2015; Besada & Nosent, 2012; Beyer et al., 2011;

	Christidis et al., 2011; Işik et al., 2013; Kieffer et al., 2014; Lurati et al., 2012; Oliveira et al., 2014; Pazzola et al., 2013; Salvarini et al., 2012; Sciascia et al., 2011; Seitz et al., 2011; Unizony et al., 2012; Vinicki et al., 2017; Vinit et al., 2012; Vionnet et al., 2017). These were not provided in our original submission as they are considered a lower level of evidence than randomised data. Nevertheless, they offer useful insight and clear trends into the length of time patients have been treated with tocilizumab in the real world, and also the steroid doses deemed acceptable for maintenance by clinicians for GCA patients. In these published case reports, 109 patients with GCA had been treated with tocilizumab. The key findings were: • Most (99/109) patients received tocilizumab 8 mg/kg IV every 4 weeks (Q4W) but other doses were also used • The majority of patients (98/109) received tocilizumab in combination with steroids. The dosage of steroids at tocilizumab onset varied from zero to 60 mg/day • Positive treatment effects of tocilizumab were reported for the majority of patients with clinical efficacy observed between one and three months after the first tocilizumab infusion • Tocilizumab was administered for different time periods (range 1 to 53 months), the majority of patients receiving tocilizumab for much less than one year • During treatment with tocilizumab, steroid doses were reduced down, many from ~45-60 mg/day to ~5 mg/day (some down to zero mg/day). One of the larger studies (Regent et al. 2016), following 34 patients with tocilizumab treatment, reported a mean treatment time with tocilizumab of 6.4 ± 4.5 months with a median follow-up of 13 months (range 1-48). Treatment stopped in 23 patients after a mean treatment duration of 5.6 ± 2.9 months and only 34.8% experienced a flare after a mean of 3.5 ± 1.3 months. These reports validate that clinicians believe 5-7.5 mg/day to be an acceptable steroid dose to maintain patients on following treatment with tocilizumab. This is consistent with the EULAR taskforce (Strehl et al. 2016) as described in Comment 5. **7.6 Summary** Roche disagrees with the Committee that all patients would need to be treated with tocilizumab for two years or more. We consider that treatment with tocilizumab for up to 12 months would be highly beneficial for GCA patients, both in terms of inducing sustained remission and reducing cumulative steroid burden. This position is supported by expert clinical opinion, as a judicious use of NHS resources. We request that the Committee's consideration reflects this stance. Consequently, our revised cost-effectiveness model, described in Comment 8, incorporates 12 months of tocilizumab therapy for relapsed/refractory patients.
8	**Revision of the cost-effectiveness model** **8.1 Appraisal reference** In Section 3.14 of the ACD, NICE states: "The company's base-case deterministic incremental cost-effectiveness ratio (ICER) for the overall population was £28,272 per quality-adjusted life year gained (QALY). The ERG's base-case probabilistic ICER was £65,801 per QALY gained... The committee preferred the ERG's base-case estimate, because it reflected some of its preferred assumptions." "The ERG's base case did not address the uncertainties arising from the fact that the 52-week steroid taper used in the comparator arm of the trial does not reflect clinical practice in the NHS" "Having concluded that the ICER is significantly higher than the range normally considered to be a cost-effective use of NHS resources, the committee did not recommend tocilizumab." **8.2 Key points:** • Roche has revised the cost-effectiveness model to incorporate new evidence and the interpretations of the clinical experts we have consulted

- Using the ERG's model and preferred assumptions, the ICER for 12 months tocilizumab treatment for relapsed/refractory GCA patients is £30,528/QALY
  - This was not reported in the Appraisal Consultation Document although it was considered during the Appraisal Committee Meeting
- Roche identified 2 errors in the cost-effectiveness model, which have been amended
- Further amendments to the cost-effectiveness model have been made to address questions raised in the Appraisal Committee Meeting, including:
  - amending the steroid tapering regimen matching NHS practice
  - incorporating more granular management costs from market research
  - updating the costs of steroid-related AEs to 2017
  - adjusting the ERGs flare rate to better reflect GiACTA data
- These changes combined give an ICER of £18,898/QALY, including the confidential Patient Access Scheme

The model amendments and associated ICER calculations presented in Appendix 1 are made using the Committee's preferred assumptions in the ERGs model for 12 months tocilizumab treatment in relapsed/refractory GCA patients. As discussed in Comments 2 and 7, relapsed/refractory patients have the highest unmet need in GCA, with the 12 months' treatment duration having the highest internal validity as this matches the GiACTA trial data.

All ICERs presented in Appendix 1 include the confidential Patient Access Scheme (PAS) for tocilizumab.

Summary

Additional, relevant evidence has been incorporated into the cost-effectiveness model to support NICE in forming reasonable interpretations and sound and suitable guidance to the NHS regarding tocilizumab to treat GCA patients. This additional evidence gives an ICER of £18,898 for relapsed/refractory patients with 12 months of tocilizumab treatment.

We trust that the information provided herein will allow NICE to reconsider its provisional recommendation and allow access to tocilizumab on the NHS.

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Insert extra rows as needed

British Society for Rheumatology Response to NICE Consultation for Tocilizumab in Giant Cell Arteritis

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Consultant Rheumatologist [redacted]
[redacted] UK GCA Consortium 2007 – [redacted] MRC Treatment According to Response in Giant cEll arteritis (TARGET) Partnership 2017 – [redacted] UK and Ireland Vasculitis Group 2016 – [redacted] Vasculitis UK 2014

[redacted]

In response to the NICE appraisal of Tocilizumab in Giant Cell Arteritis (GCA), the British Society for Rheumatology (BSR) would like to address some important issues raised in the consultation document. Below are some direct responses, followed by a more extensive review of the relevant evidence, and concluded with a proposal on the use of Tocilizumab in certain clinical scenarios.

BSR Feedback summary

BSR feels that GCA subgroups such as patients with disease relapsing/refractory to glucocorticoids (GC) and those with contra-indications to long term GC therapy have not been separately considered in this NICE consultation. Treatment with Tocilizumab of this sub group may be efficacious, safe and cost effective since the costs averted of GC toxicity, ischemic complications, vascular damage, cardiovascular and cerebrovascular events are high.

A literature review follows which details sub groups of GCA, the unmet treatment need in relapsing/refractory patients, their large GC burden with the resulting serious toxicities such as diabetes, hypertension and fragility fractures. Consequences of damage due to vascular inflammation uncontrolled by GC, such as aortic aneurysms, aortic dissection and rupture, large vessel stenosis and occlusion, sight loss and other ischemic complications are also reviewed.

The patient perspective is highlighted throughout the review using illustrative case histories.

BSR proposes that relapsing/refractory patients, often with large vessel vasculitis, and patients with GC related contraindications may be treated with weekly injections of 162mg Tocilizumab for 12 months along with GC doses tapering to less than 5mg at around 6 months provided disease activity remains controlled. Patients who have severe and/or extensive disease at disease onset (such as those with ischaemic symptoms or features of proven LV-GCA) should also be eligible for Tocilizumab treatment for 12 months.

BSR feels that the management of relapsing or refractory GCA requires further evidence. It offers to work with NICE on a research agenda directed at efficacious and safe treatment of this particularly difficult sub-group, with careful documentation of outcomes and GC toxicities.

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

The BSR would argue no.
In the final recommendations, no clear distinction has been made between the different subsets of GCA. This is despite the consultation document referring to this accepted clinical delineation further on. It is widely accepted that GCA has different subsets; those with purely cranial disease, those with more widespread vascular involvement termed Large Vessel-GCA (LV-GCA), and those with glucocorticoid (GC) refractory and relapsing disease. It is these last 2 groups as well as in patients with co-morbidities or pre-existing adverse effects that may be exacerbated by GC, who are in desperate need of additional treatment options, who need to be considered for Tocilizumab treatment rather than the GCA cohort as a whole. The NICE consultation does not appreciate that the cumulative GC use in these subsets is greatly increased, resulting in significant clinical and economic burden. **We explore these areas in greater detail below.**

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

   The summaries do not consider the fact that, as with other inflammatory conditions where biologic agents are used, GCA exhibits a range of severity and disease extent. Severe and extensive GCA is unresponsive to GC unless they are maintained long term at doses associated with major toxicity. Severe and extensive GCA is also associated with a higher likelihood of ischaemic complications, vascular damage, including aortic dilatation, and cardiovascular events. Costs averted with efficacious therapy with Tocilizumab in this sub group are the costs of treating serious GC toxicity, vascular damage, cardiovascular and cerebrovascular events **(see review below for details)**. In this sub group of relapsing/refractory patients the cost-effectiveness estimate of Tocilizumab therefore may be much lower.

   The summaries also assume that GC are tapered in all cases of GCA to zero. This is not the normal rheumatological practice in treatment of other vasculitides and connective tissue diseases where patients are often maintained on low dose GC (< 5 mg daily) along with adjunctive conventional or biologic disease-modifying anti-Rheumatic Drug (c or bDMARD) therapy. Using this model patients with GCA may not require Tocilizumab treatment for greater than 12 months again significantly reducing the cost effectiveness estimate (for details see below). There are no cDMARDS with high quality evidence for efficacy in GCA.

3. **Are the recommendations a sound and suitable basis for guidance to the NHS?**

The BSR would argue no.

Tapering GC alone may be acceptable for some patients, this is not disputed. However, for LV-GCA and relapsing groups, who by very definition are refractory to GC, there is no proven role for cDMARDs as steroid sparing agents. By not recommending Tocilizumab for these difficult to treat subsets, NICE still leaves an unmet need for efficacious treatment. For these patients, there are no current effective therapies available.

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

These recommendations may be construed to discriminate against older people and against people who currently have no choice but to take long term steroids for disease control.

GCA is a disease of older people, typically affecting people from the age of 50 with a peak incidence some decades later. This is the only vasculitis that is almost exclusively treated with GC monotherapy, due to a lack of treatment alternatives. Age is almost certainly a factor in the historical paucity of clinical trials and high quality clinical data, yet older patients are in the greatest need of GC-sparing medications due to the high GC doses required and higher number of co-morbidities. For patients with osteoporosis, congestive cardiac failure and type II diabetes – the commencement of high-dose prednisolone always means worsening of their other co-morbidity. These patients have no other treatment options. As such, limiting treatment options could be seen to discriminate based on age. Additionally, although GCA predominantly affects older people, many patients with LV-GCA are younger and may still have over a decade left of their working life. Not giving these patients a reasonable treatment alternative is condemning them to a lifetime of significant disability and early unemployment.

As we have previously alluded to and explain in more detail in our attached review, those with LV-GCA and GC refractory and relapsing disease are more likely to have increased cumulative GC burden and uncontrolled vascular inflammation. High GC use results in significant disability and co-morbidity, including obesity, diabetes, hypertension, cardiovascular and cerebrovascular events, osteoporosis and fracture, sarcopenia, peptic ulcer disease, ophthalmic complications, adrenal insufficiency and death. Uncontrolled inflammation also increased the risk of direct vascular complications such as aortic aneurysm, dissection and rupture, vascular stenosis, heart failure, valvular regurgitation, peripheral vascular disease, sight loss and cerebrovascular events. These are not only expensive to treat, but have significant adverse effects on quality of life and independence.

Further comments and rebuttal
(Comments specifically on paragraphs 1.2, 3.1, 3.5 and 3.7).

1.2 The health economic assessment assumed that Tocilizumab would be used for 2 years and concludes that for the average patient with GCA this fails to meet the NICE QALY threshold. The disutility of GCs in the company model was mainly driven by risks of diabetes and fracture. This is an average across the entire population of GCA. For high-risk subgroups (e.g. those who have already had relapses and fragility fractures while on GCs) the disutility of GC therapy is far higher as has been clearly outlined in the above review. This has not been incorporated into the model.

3.1 The interpretation of the clinical experts' advice is that it is difficult to identify at disease presentation which patients are going to relapse or not. While this may be true, relapsing GCA is a recognised clinical subset and there is general agreement on its features. It is an error of logic to say

that because patients with relapsing GCA cannot be reliably identified at disease onset at the group level, they cannot be identified on follow-up. Surely an individual patient with relapsing GCA can be identified reliably by the fact that they have GCA and have had relapses. This is the subgroup with the greatest GC burden, greatest cumulative risk of GC-related complications and probability of vascular damage. It is easy to identify (as outlined above) this subset that would benefit most from Tocilizumab. This group of patients should not be disadvantaged because less severe and less extensive GCA can be managed with lower GC-related toxicity, particularly when no treatment alternatives currently exist.

3.5 The 52-week taper recommended by BSR guidelines is a starting-point for clinicians to work from, rather than a description of what actually happens. The guidelines also state that if patients relapse during taper then the dose of GC escalates and this necessarily lengthens the total duration of GC therapy. The reason why GC are tapered over 18-24 months in clinical practice is because patients often relapse during taper. The trial protocol was designed to reflect this practice – with a starting-point of a 52-week taper, but with GC dose escalated in the event of relapse. This was indeed observed in the GiACTA placebo arm in which the GC dose was escalated in many patients due to relapse. Therefore, we would argue that the "52-week taper placebo arm" is not really just 52 weeks of GC and does indeed represent current clinical practice in England. We feel it is an appropriate comparator and it does not bias the results of the trial.

3.7 The reason the trial did not show a difference in the rate of GC related adverse events (GC-AE) was that as an efficacy trial it was not powered to show a difference in such rates. Therefore, absence of evidence of a reduction of GC-AE cannot be taken as evidence that Tocilizumab does not reduce the risk of GC-AE. It is far more likely that because GC-AE are known to relate strongly to cumulative GC dose, the reduction in cumulative GC doses observed in the Tocilizumab arms of the trial is likely to translate to lower long-term risk of GC-AE in GCA patients treated with Tocilizumab.

Proposal:

We suggest that based on the literature review and results of trials of Tocilizumab in GCA, including GiACTA, that Tocilizumab has a major role in efficacious and safe management of severe, relapsing and refractory GCA, particularly in those with extensive disease such as LV-GCA, or those with direct vascular complications of uncontrolled disease. Relapsing or refractory disease is defined as relapse on doses >5mg prednisolone daily despite use of the recommended BSR dose reduction regimen.

It also has a major role as outlined in our figure, in patients with co-morbidities that may be exacerbated by long term GC therapy or in the presence of GC related serious adverse effects. We propose that patients in these sub-groups are treated with weekly injections of 162mg Tocilizumab for 12 months along with GC doses tapering to less than 5mg in around 6 months provided disease activity remains controlled. Patients who have severe and/or extensive disease at disease onset (such as those with ischaemic symptoms or features of proven LV-GCA) should also be eligible for Tocilizumab treatment for 12 months.

We recommend the tapering regimen should be individualised. Possible scenarios for how this could be achieved are outlined below:

In patients without ischaemic symptoms, such as jaw claudication or amaurosis fugax on relapse: Prednisolone 20mg daily for 4 weeks, 17.5mg daily for 4 weeks, 15mg daily for 2 weeks, 12.5mg daily for 2 weeks, 10mg daily for 4 weeks, 7.5mg daily for 4 weeks, 5mg daily for 4 weeks thereafter reducing by 1mg every 2-4 weeks in an attempt to achieve the lowest GC dose while maintaining disease remission.

In patients with ischaemic symptoms at relapse, higher starting doses of prednisolone will be required (40-60mg).

This treatment regimen would allow an additional 6 months treatment with weekly Tocilizumab monotherapy, while on lowest possible dose of prednisolone, to sustain remission. At 12 months Tocilizumab treatment could be stopped for patients in remission.

Thereafter, we would recommend individual treatment decisions are taken by the supervising clinician as to whether GC can be stopped altogether or continued at an acceptable low dose (<5mg prednisolone per day) with or without additional immunosuppression for remission maintenance. The scenario could include provision of a second 3 to 6 months course of Tocilizumab therapy in case of a further relapse.

Our current position on management of relapsing or refractory GCA requires further evidence base. We recommend a research agenda directed at efficacious and safe treatment of this particularly difficult sub-group, with careful documentation of GC toxicities. This may need to include randomised controlled trials of promising c-DMARDs either to induce or maintain remission in GCA.

Literature Review: The unmet need and case for targeted more efficacious therapies in Giant Cell Arteritis – Large Vessel Vasculitis, with clinical and cost implications of refractory/relapsing disease

Large vessel vasculitis (LVV) can be thought of as a spectrum of disease including GCA, Takayasu arteritis (TAK) and Polymyalgia Rheumatica (PMR) (Dejaco et al. 2017). Subsets of GCA patients have more extensive large vessel involvement, termed LV-GCA. These patients are usually identified because they are GC refractory and difficult to treat, with higher rates of flares and more predominant constitutional symptoms. Observational cohort studies report flares in 34-62% of GCA patients, with only 15-20% achieving sustained remission with GC alone (Dejaco et al. 2017). Investigating this refractory group for evidence of widespread vascular inflammation is becoming easier with improvements in imaging techniques, for example FDG-PET/CT. Currently 12-37% of GCA patients have evidence of LVV on imaging depending what is used (Petri et al. 2015).

CASE 1: Cranial GCA relapsing as LV-GCA
75 year-old woman presented with typical symptoms of cranial GCA, with positive temporal artery biopsy. After an initial good response to high dose GC she started to develop relapse of symptoms on weaning down to 10mg prednisolone and below. With this her inflammatory markers rose substantially (CRP 111). At this point axillary and subclavian ultrasound showed increased intimal-medial thickness (IMT) (Fig 1). FDG-PET/CT also showed extensive FDG uptake in the axillary vessels, aorta and common iliac vessels. This case illustrates how failure to settle in GCA can be a clue to the development of LVV.

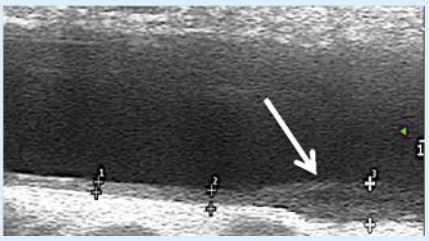

Fig 1. Thickened IMT of subclavian/axillary artery (arrow)

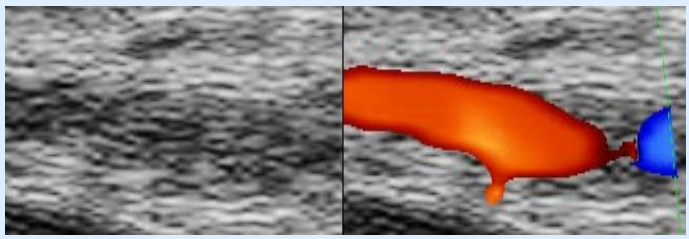

Fig 2. Comparison to normal temporal artery

GiACTA baseline data (Tuckwell et al 2016) Of 251 patients, 119 (47%) had newly-diagnosed and 132 (53%) had relapsing GCA. Mean age was 69 years in both subsets; 75% were women. More than one-third of patients were enrolled in GiACTA based on findings of large-vessel imaging studies alone. A high percentage of the patients enrolled (17% of the overall cohort) were classified as having disease refractory to GC. These patients were judged by their physicians never to have been in remission, despite courses of GC usually considered sufficient for remission induction. Although the conventional wisdom regarding the responsiveness of GCA to GC is that the disease responds dramatically to GC initiation, these data suggest that a sizeable subset of patients respond less robustly, and that in fact many patients fail to achieve remission with GC alone. In PMR, some groups of patients respond less well to steroids, with only 45-55% having a complete response, and 25-27% with a partial and 15% with no response respectively (Dasgupta et al, 2012).

CASE 2: GC refractory GCA

63 year-old woman with LV-GCA was started on prednisolone 60mg at diagnosis. Trials of steroid sparing agents including Azathioprine and Leflunomide were ineffective, with continued constitutional disturbance, inability to taper GC, sustained elevated CRP 60-80 and marked GC side effects including significant weight gain and proximal myopathy. On referral for second opinion her cumulative dose of prednisolone was 11,500mg. Despite this FDG-PET/CT showed significant widespread vascular FDG uptake (Fig 1 & 2). She has since had a good clinical and biochemical response to Tocilizumab.

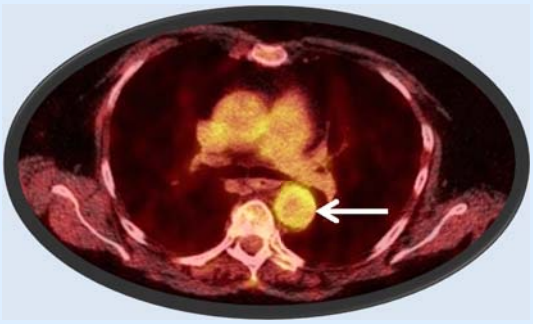

Fig 1. FDG-PET/CT showing avid FDG uptake in the aorta (arrow)

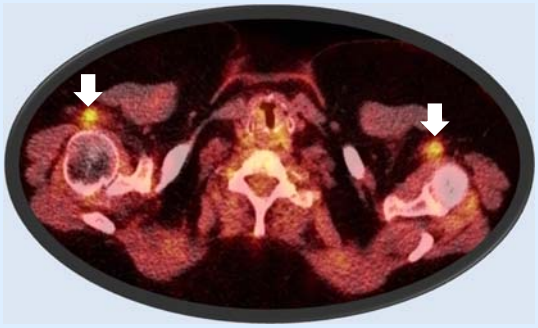

Fig 2. FDG-PET/CT showing avid FDG uptake at the axillary arteries (arrows)

As such the clinical and economic burden of those with refractory LV-GCA is more than the typical GCA cohort, requiring more frequent intervention. Figure 1 highlights the refractory patients that form the focus of this review on clinical and cost implications of treating this group with conventional GC therapy.

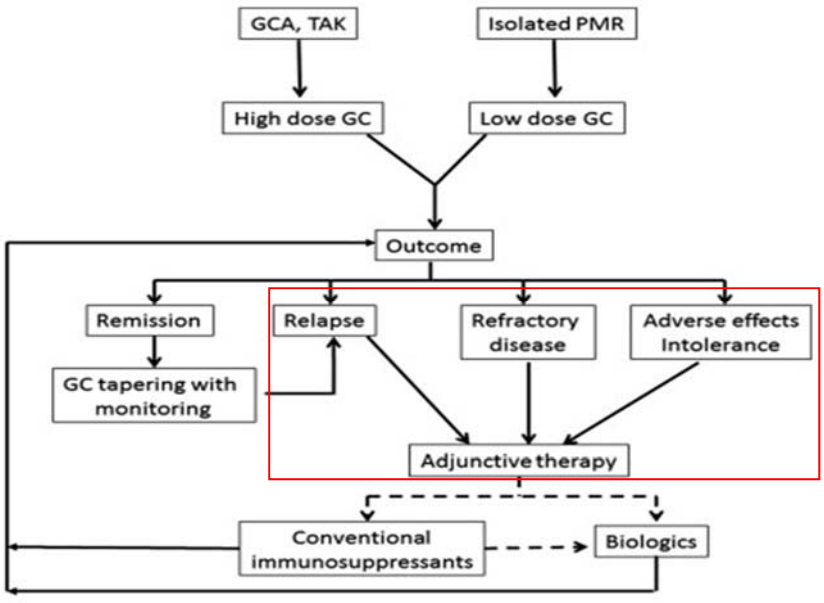

Figure 1. Adapted from Kermani and Dasgupta; Rheumatology (Oxford). 2017 Oct 24– Treatment algorithm for LVV, with the target refractory group highlighted in the red box.

Burden of diagnosis and monitoring:

Patients with refractory disease often require more frequent follow-up both in terms of clinician time and monitoring investigations (e.g. interval FDG-PET/CT for disease activity or vascular complication monitoring including aneurysms and stenosis). This clinical impression is borne out in the literature, with increased "health care resource utilization" highlighted (Rice at al. 2017). Furthermore, current estimations of clinical and economic burden may be underestimated, as many researchers in this area do not have a primary focus on GCs in autoimmune or inflammatory disease, which often requires longer-term higher doses as part of the main treatment bundle, bringing with it the associated side effects.

Although not directly affecting the NHS budget, chronic disease is known to affect work productivity. Additionally, it is a vicious cycle, whereby unemployment causes increased depression and mental health issues, with the inevitable reliance on health and social care. Although generally a disease of older people, GCA does affect people typically from the age of 50, many of whom may still have over a decade left of their working life.

Burden of glucocorticoid side effects:

Patients with refractory disease are, by definition, poor responders to GC, with frequent relapse and flare. As such they require much higher and prolonged courses whilst an effective steroid-sparing agent is sought, with higher cumulative doses. In GCA patients typically exceed a cumulative dose of 5000mg prednisolone over several years (Broder et al. 2016). It is estimated for every 1000mg cumulative increase in GC dose, the adverse event hazard ratio increases by 3% (Broder at al., 2016). Unfortunately, this does not completely treat the underlying inflammation and contributes to a higher incidence of steroid related side effects, estimated to affect 85% of LV-GCA patients (Dejaco et al. 2017). This cohort is particularly vulnerable due to additional factors of older age and higher prevalence of co-morbidities. In a large UK retrospective study the average cumulative prednisolone use over the first 2 years from diagnosis was 8600mg, however 33.4% received over 10,000mg and 3.3% more than 25,000mg (Petri et al. 2015). A review by Manson et al. estimates the annual excess cost of treating GC related effects is at least an extra £84.2 million per year to the NHS (Mason et al. 2009). Recently a consensus based GC toxicity index has been published (Miloslavsky et al. 2016), which could be used to more carefully document the burden of GC toxicity in these patients.

EULAR taskforce recommendations suggest that the risk of harm is low for the patients at long-term dosages of ≤5 mg prednisone equivalent per day, whereas at dosages of >10 mg/day the risk of harm is elevated (Strehl et al. 2016). Between 5 to 10mg the risk of harm is dependent on additional patient specific factors. Results of meta-analysis of ANCA-associated vasculitis suggest that long-term maintenance using continuing low dose GC therapy significantly decreases disease activity without adding to the GC toxicity burden (Schönermarck et al. 2014). This practice could sensibly be extrapolated to relapsing and refractory GCA after achieving disease control.

Some of the more commonly encountered problems are discussed below.

- **Diabetes, Obesity and the Metabolic Syndrome** – The estimates of incidence in the GC population vary, but is universally agreed to be clinically significant. Up to a four-fold increased frequency of hyperglycaemia and diabetes has been observed with GC use (Sarnes et al. 2011). In a retrospective study of GC effects in a GCA population, the incidence of new-onset diabetes increased by 5% for every cumulative 1000mg increase (Broder et al. 2016). The additional

annual cost of each new case per year was estimated at £2,519.86 per patient (Mason et al. 2009). Diabetes is also a risk factor for cardiovascular and cerebrovascular disease, which exacerbate the health and financial costs. This is reflected in the GiACTA baseline data.

GiACTA baseline data (Tuckwell et al 2016) Patients with relapsing GCA were substantially heavier than those with newly diagnosed disease by an average of 5.2 kg [SD, 14.9]. When baseline weights were stratified by sex, women with relapsing disease, on average, weighed 4.2 kg more [95% CI, 0.49-7.87; p=0.027] and had higher BMI (1.7 kg/m2 higher [95% CI, 0.44-2.99; p=0.009] than women with newly-diagnosed GCA. Men with relapsing GCA weighed, on average, 8.2 kg more [95% CI, 1.42-15.09; p=0.019] and had a higher BMI (2.9 kg/m2 higher [95% CI, 0.32-5.37; p=0.028] than their counterparts with newly-diagnosed GCA. Patients with relapsing disease also had a higher baseline prevalence of depression (16% vs 4%; p=0.002) and higher baseline prevalence of osteopenia/osteoporosis (33% vs 23%; p=0.062). Other co-morbidities were higher in the baseline group without being statistically significant.

The higher weight and body mass index (BMI) measurements among patients with relapsing disease are particularly striking because of the overall health implications of becoming overweight or obese (Poirier et al. 2006). These differences are likely to be even more pronounced in community-based populations of GCA patients, because patients with newly diagnosed GCA in this trial could have received up to 6 weeks of prednisone therapy before their baseline weight measurement. Had the weight measurement been taken before starting GC, the disparity in weight between the relapsing and newly diagnosed subsets would have been even larger.

- **Hypertension** - Hypertension occurs in over 30% of patients on long-term GC (Rice at al. 2017). Public Health England states the cost of treating hypertension and its complications costs the NHS over £2 billion every year from 2014 data, and there is potential 10 year savings of £850 million to the NHS and social care budget if hypertension is better controlled (PHE 2014). NICE estimates that pharmacological treatment of hypertension accounts for £1 billion of Primary Care expenditure (NICE CG127). The high costs associated with hypertension are not surprising considering the impact it has on development of other conditions such as renal impairment, cardiovascular and cerebrovascular diseases.

- **Cardiovascular and cerebrovascular disease** – Patients on GC have an increased risk of cardiovascular and cerebrovascular events, including myocardial infarction, stroke and vascular dementia. The overall estimated prevalence is 4% in those on long-term GC (Rice at al. 2017). A dose dependant relationship has also been observed with this as well, with a 2.15 risk ratio of acute myocardial infarction (95% CI 1.9-15.5) for daily prednisolone doses higher than 10mg. There is evidence that this increased risk reduces with reduction and cessation of GC, with Sarnes et al. identifying that this would avoid 19.4 myocardial infarctions per 10,000 population, with a cost saving of $513,553 (£385,714 at current exchange rate 2017) at the time of publication (Sarnes et al. 2011). Therefore, there are considerable clinical and economic gains to be made by using efficacious GC sparing agents in GCA.

- **Osteoporosis and Fracture** – Approximately 536,000 new fragility fractures occur in the UK each year, with an estimated cost of £4.4 billion each year to the NHS (Compston et al. 2017). The risk of osteoporotic fracture is exacerbated for those on long-term GC with a dose dependant effect. The fracture risk is increased in those on high compared to low dose GC, with a relative risk of hip fracture of 2.21 (95% CI 1.85-2.64) in those on prednisolone at doses of 7.5mg per day or more, compared to those below (van Staa et al. 2000), rising to 3.13 (95% CI 1.49-6.59) for doses above 30mg (de Vries at al. 2007). Patients with refractory LV-GCA are particularly susceptible, since high dose GC therapy is commonly used in this subgroup. The average cost of

care for a hip fracture secondary to GC is estimated at £10,761 (Kanis et al. 2007). The United Kingdom mortality rate from hip fracture was 6.7% in 2016, with an average of 21.6 days in hospital, an increase on the previous year equating to an extra 160 beds in England (National Hip Fracture Database Annual Report 2017). Pharmacological fracture prevention treatments are essential, but these too are estimated to cost £84 million – a cost which could be reduced in those able to wean their GC to a lower dose or off completely (Svedborn et al. 2013).

- **Peptic ulcer disease** is known to be increased in patients on long term GC, hence the recommendation to try and attenuate this risk with proton-pump inhibitor protection where there are no contraindications to doing so. Even so, there is a reported increased relative risk of 2.0 (Mason et al. 2009). There are additional costs incurred while investigating disease including gastroscopy, a procedure for which there is excessive demand within the NHS.

- **Ophthalmic complications** – Includes cataracts, ocular hypertension, and open-angle glaucoma. An increased risk of cataracts is seen even at a relatively lower dose of 5mg prednisolone (Sarnes et al. 2011). This adds weight to the concept of 'no safe dose of steroid', and should prompt efforts to wean down to safe doses as much as is possible.

Other well-recognised side effects are not as easy to quantify in terms of cost, but have a significant clinical burden. Prolonged GC use, leads to adrenal suppression, and features of Cushing's syndrome. This is responsible for the 'moon face', central adiposity and intra-scapular fat deposition which coupled with weight gain causes great distress to patients. Effects on the hypothalamic-pituitary-adrenal axis are also thought to be the root cause behind neuropsychiatric changes, which can range from low mood and depression to psychosis (Sarnes et al. 2011).

Direct vascular complications of uncontrolled disease:

- **Aortic Aneurysms** – The LV-GCA cohort are at increased risk of aortic aneurysms, with a large UK cohort study reporting more than two-fold increased risk (Robson et al. 2013). Individual cohort studies have found the risk of thoracic aneurysm is even higher, with a seventeen-fold increase reported in LV-GCA patients (Gornik and Creager, 2008). Of concern 82% of the thoracic aneurysms in this American cohort developed after diagnosis, at a median follow-up of 5.8 years, showing GC had not prevented this (Evans et al. 1995 and Case 3). Currently up to 10% of abdominal aortic aneurysms are thought to be inflammatory (Stone and Frankhauser, 2012). The cause of inflammation is multifactorial, but includes evidence of an IL-6 driven mechanism, a pro-inflammatory cytokine implicated in GCA (first report Dasgupta and Panayi, 1990). In a study by Jones et al. evaluating abdominal aortic aneurysm and IL-6, higher levels were detected close to the aneurysm as sampled from the iliac artery, compared to a distal site at the brachial artery (Jones et al. 2001). This difference was higher in patients with greater aneurysmal wall thickness and confirmed histological inflammation, suggesting the aneurysm itself may be an important source of IL-6 (Jones et al. 2001).

  In terms of when to intervene surgically, there is evidence that once above 3.5cm in diameter the annual risk of rupture, dissection or death is 7.2%, rising to 14.1% when it reaches above 6.0cm (Chau et al. 2013). A retrospective cohort study by Pape et al. showed concern that current thresholds for surgery were not low enough, with a significant level of risk in those with aneurysmal diameter less than 5.5cm (Pape et al. 2007). The cost of surgery itself is approximately £9893 for open repair and £10,416 for Endovascular Stent-Graft Repairs (EVAR) form 2009 NICE costing data (NICE Costing Statement: EVAR to the treatment of abdominal aortic aneurysms, February 2009). In a retrospective Norwegian study of 24 patients undergoing

thoracic aortic aneurysm repair the average length of stay was 5 days for proximal disease and 10 days for distal disease, with 2 and 4 days respectively taking place in an intensive care setting (Mishra et al. 2008). The cost of these stays averaged at 19 803USD and 23000USD (£14820 and £17213 at current exchange rate 12/12/17) (Mishra et al. 2008). These are projected costs related to aneurysms as a group. Inflammatory aneurysm surgery is known to carry a higher complication rate and consequent cost, with higher rates of limb stenosis and occlusion, on-going inflammation and fibrosis of peri-vascular tissue, which is of particular concern when involving the ureters, with higher operative mortality (Stone and Frankhauser, 2012). In particular open surgical repair is associated with a 3-fold increase in mortality rates (Stone and Frankhauser, 2012).

CASE 3: Aortic Aneurysm in PMR-LVV

70 year old woman with a 7 year history of PMR and frequent clinical relapses was diagnosed with LVV and ascending aortic aneurysm. Her cumulative dose of prednisolone on referral was 30,000mg. Despite this high GC intake the FDG-PET/CT showed an ascending aortic aneurysm (Figure 1) with high FDG uptake (Figure 2), suggesting it is a complication of uncontrolled disease activity. She responded to the open-label phase of SIRRESTA study (Sirukumab, anti-IL-6, in GCA trial).

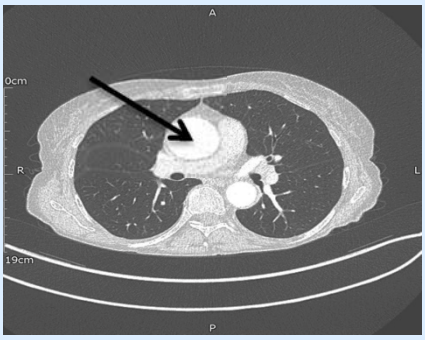

Fig 1. Cross-section of contrast CT showing ascending aortic aneurysm (arrow)

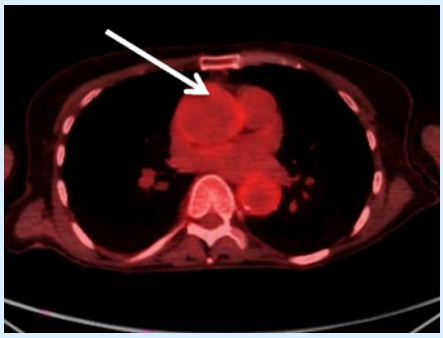

Fig 2. FDG-PET/CT showing high FDG uptake in the wall of the ascending aortic aneurysm (arrow)

- **Aortic Dissection and Rupture –** Evidence shows that those with uncontrolled inflammation in LVV have a higher risk of dissection and rupture. In a retrospective cohort analysis of LV-GCA patients by Kermani et al. 4 of 7 patients with aortic dissection or rupture had histological evidence of active inflammation, compared to none from 7 patients with aneurysm but no dissection or rupture (Kermani et al. 2016). For patients with acute aortic dissection surgical intervention is still the primary management strategy for most. Long-term registry data shows an increased trend towards surgical intervention for both type A and B dissections (Pape et al. 2016). Endovascular repair would be the method of choice compared to open repair, however this still carries a significant cost tariff (Luebke and Brunkwall, 2014). In patients with rupture, both medical and surgical treatment pathways carry significant in-hospital mortality rates and long hospital stays, 58% and 26% respectively (Chau et al.). Even if a patient survives, the long-term outcomes are poor, since 40% may have a further rupture or require further interventions (Chau et al.). Preventing aneurysms getting to the point of rupture is both clinically and

economically advantageous. One retrospective study of abdominal aortic aneurysm by Tang et al. found rupture repair costs 4 times more than planned elective surgery, with a mortality rate of 18% compared to 1.6% respectively in their cohort (Tang et al. 2003).

CASE 3: Aortic Dissection in LVV

66 year-old woman with aortitis and mural ulcer with dissection flap over the posterior aspect of descending thoracic aorta on CTA (Figure 1). Treated with methylprednisolone pulse followed by oral prednisolone and Tocilizumab with good clinical and radiological response as demonstrated below (Figure 2).

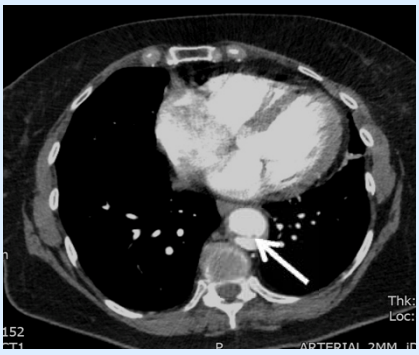

Fig 1. Dissection flap over posterior aspect of descending thoracic aorta (arrow)

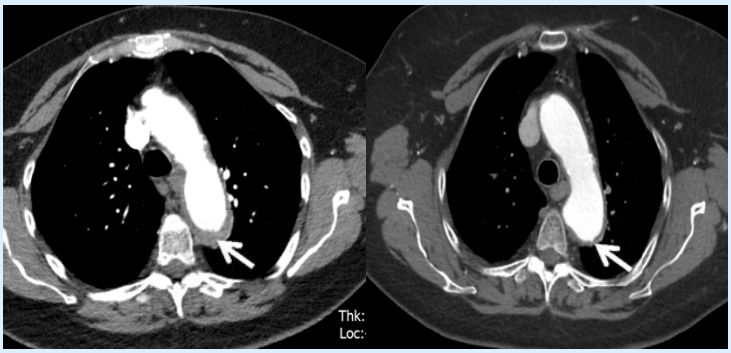

Fig 2. RIGHT IMAGE – CT prior to TCZ with aortic thickening (arrow), LEFT IMAGE – CT 1 year post TCZ with marked improvement.

- **Large vessel stenosis and angioplasty/stenting/re-vascularisation procedures–** It is well known that large vessel vasculitis is a spectrum of disease, encompassing GCA, LV-GCA and TAK. A known complication is stenotic and occlusive disease. Stenotic disease in vasculitis is associated with morbidity, with 60% being limited in their daily activities (Perera et al., 2013). This can progress to a point of critical limb ischaemia, where surgical intervention is often necessary to prevent necrosis, gangrene and amputation. The costs may not end here, as restenosis is common, and requires on-going clinical and radiological follow-up (Perera et al., 2013). If suitable agents are utilised medical revascularisation is possible. A report by Evans et al references a case where use of Tocilizumab restored flow to the axillary artery in a patient with LVV, whilst weaning down to a dose of 3mg prednisolone (Evans et al., 2016).

CASE 4: PMR-LVV with limb claudication secondary to stenosis

66 year-old man presented to his local hospital with polymyalgic and constitutional symptoms. FDG PET/CT confirmed LVV (Figure 1). He was referred for second opinion due to poor GC response and development of new symptoms including left upper limb claudication. Ultrasound showed intimal thickening and stenosis of the axillary arteries (Figure 2).

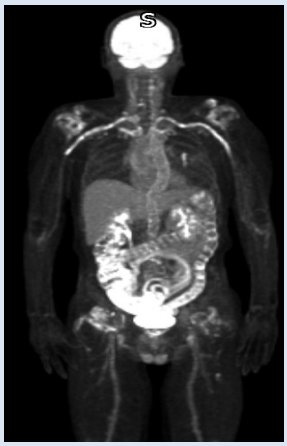

Fig 1. FDG-PET/CT showing widespread vascular high FDG uptake

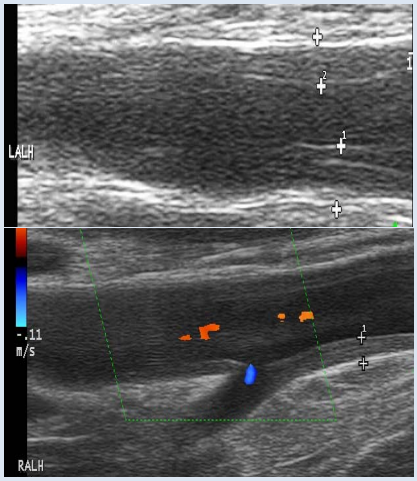

Fig 2. Ultrasound of the left (top) and right (bottom) axillary arteries with increased IMT and stenosis

- **Heart failure** - Even before the point of aneurysmal rupture, the natural history of untreated disease is known to include aortic root dilatation, valvular regurgitation and heart failure. Heart failure is costly to treat, both in the outpatient and inpatient setting. It is estimated approximately 5% of all acute admissions in Europe are secondary to heart failure (Braunschweig et al. 2011). Estimates put annual NHS expenditure on heart failure at 2% of the entire budget, with over 1 million inpatient bed-days per year (National Heart Failure Audit 2013).

- **Valvular regurgitation** – As aforementioned it is known that proximal aortic root dilatation can result in severe and symptomatic valvular regurgitation (Muraru et al. 2016). Although replacement procedures are surgically possible, they are associated with high levels of morbidity and mortality, as well as high costs due to significant peri-operative risks including acute renal failure, subdural haematoma, prolonged intensive care stays and potential future procedures such as pacemakers (Sung et al. 2009).

- **Peripheral Vascular Disease** – LVV is associated with the risk of peripheral vascular disease (PVD) with a hazard ratio of 2.5 (95% CI = 1.53-4.08). It is postulated that this is due to a combination of direct inflammation and accelerated atherosclerosis (Borg and Dasgupta, 2009).

- **Sight loss** – It is estimated 10-25% of GCA patients present with visual complications (Dasgupta et al. 2016). Of these, irreversible sight loss remains a significant cause of morbidity amongst the GCA population. This entails large, personal, healthcare, social care, direct and indirect family costs. The introduction of 'Fast Track Pathways' aiding prompt diagnosis and treatment has reduced its incidence from 37% to 9% in those services, but unfortunately this is not universal practice (Patil P. 2015).

- **Cerebrovascular disease** – evidence from the UK Clinical Practice Research Datalink 1991-2010 shows GCA patients are increased risk of cerebrovascular events compared to age, sex and location matched controls, with a hazard ratio of 1.45 (95% CI 1.31-1.60) (Robson et al. 2016).

CASE 5: Sight loss in GCA
A 75 year-old woman repeatedly attended the Emergency department with headache after a minor injury. A diagnosis of GCA was only made after irreversible sight loss (Figure 1) and scalp necrosis (Figure 2).

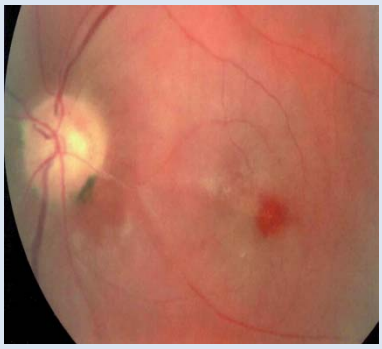

Fig 1. Retinal image following irreversible sight loss in GCA

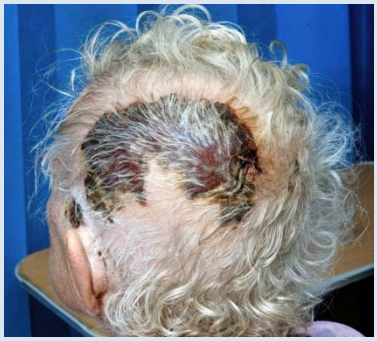

Fig 2. Scalp necrosis in GCA

Role of Conventional Disease Modifying Anti-rheumatic Drugs (cDMARDs) or other biologics in GCA

There is no proven role for cDMARDs as steroid sparing agents in GCA.

There is one meta-analysis based on three small RCTs that suggests 7.5-15mg Methotrexate (MTX) weekly has a small steroid sparing effect over the course of the disease (Mahr 2007) so its use is suggested in high risk GCA in the 2010 British Society of Rheumatology (BSR) guidelines, but the 2016 BSR GCA Literature Review Team have objectively re-reviewed the data and have concluded:

- The meta-analysis showed a lower probability of relapse at 12-24 months BUT
- No difference in cumulative GC doses or duration of GC therapy (unlike Mahr 2007)
- No difference in mortality, vision loss, malignancy, infections, psychiatric side effects, fractures, cataract, diabetes, hypertension, cushingoid habitus, weight gain and skin fragility
- Higher probability discontinuation MTX than placebo due to side effects.

One small randomised controlled trial (RCT) of Azathioprine in GCA cannot be interpreted, as there was a 44% drop out rate in the treatment group. Other agents such as leflunomide, mycophenolate and cyclosporine have shown promise in case series, but have not been tested in RCTs. Cyclophosphamide had a high rate of toxicity in the age group affected by GCA.

A few small RCTs have found that tumour necrosis factor (TNF) inhibitors are ineffective.

Role of Tocilizumab in GCA:

The role of Tocilizumab in GCA now has a good evidence base. A phase II study with 52-week follow-up suggested higher remission rates and lower cumulative GC doses following use of intravenous Tocilizumab in combination with a short cycle of GC compared to placebo (Villiger et al. 2016). In

the phase III trial (GiACTA) 119 newly diagnosed and 132 relapsing patients were randomised to receive either weekly or fortnightly subcutaneous Tocilizumab, both with a 26-week prednisolone GC taper, versus placebo arms with a 26 and 52 week Prednisolone taper alone (Stone et al. 2017). Sustained prednisolone-free remission (absence of relapse and normal CRP) was achieved in 56% and 53% of the weekly and fortnightly Tocilizumab groups, respectively, compared to only 14% and 18% in the 26 week and 52 week Prednisolone taper placebo arms respectively. In the Tocilizumab arms the cumulative GC dose was over 40% lower than the placebo prednisolone only arms, with a lower incidence of adverse events (14-15% in Tocilizumab arms versus 22-26% in placebo group). From these results Tocilizumab has been licenced for use in GCA by the FDA.

CASE 6: GC resistant sight threatening GCA

A 69 year old woman with osteoporosis was diagnosed with biopsy positive GCA after presenting with symptoms suggestive of impending bilateral blindness, including episodes of double vision and bilateral transient visual loss. Despite over two months of >1mg/kg prednisolone, repeated methylprednisolone pulses and Methotrexate, episodes of bilateral visual blurring continued. After commencing Tocilizumab, the visual symptoms resolved and the prednisolone dose has been successfully reduced without GCA flare.

Proposal:

We suggest that based on the literature review and results of trials of Tocilizumab in GCA, including GiACTA, that Tocilizumab has a major role in efficacious and safe management of severe, relapsing and refractory GCA, particularly in those with extensive disease such as LV-GCA, or those with direct vascular complications of uncontrolled disease. Relapsing or refractory disease is defined as relapse on doses >5mg prednisolone daily despite use of the recommended BSR dose reduction regimen.

It also has a major role as outlined in our figure, in patients with co-morbidities that may be exacerbated by long term GC therapy or in the presence of GC related serious adverse effects. We propose that patients in these sub-groups are treated with weekly injections of 162mg Tocilizumab for 12 months along with GC doses tapering to less than 5mg in around 6 months provided disease activity remains controlled. Patients who have severe and/or extensive disease at disease onset (such as those with ischaemic symptoms or features of proven LV-GCA) should also be eligible for Tocilizumab treatment for 12 months.

We recommend the tapering regimen should be individualised. Possible scenarios for how this could be achieved are outlined below:

In patients without ischaemic symptoms, such as jaw claudication or amaurosis fugax on relapse: Prednisolone 20mg daily for 4 weeks, 17.5mg daily for 4 weeks, 15mg daily for 2 weeks, 12.5mg daily for 2 weeks, 10mg daily for 4 weeks, 7.5mg daily for 4 weeks, 5mg daily for 4 weeks thereafter reducing by 1mg every 2-4 weeks in an attempt to achieve the lowest GC dose while maintaining disease remission.

In patients with ischaemic symptoms at relapse, higher starting doses of prednisolone will be required (40-60mg).

This treatment regimen would allow an additional 6 months treatment with weekly Tocilizumab monotherapy, while on lowest possible dose of prednisolone, to sustain remission. At 12 months Tocilizumab treatment could be stopped for patients in remission.

Thereafter, we would recommend individual treatment decisions are taken by the supervising clinician as to whether GC can be stopped altogether or continued at an acceptable low dose (<5mg prednisolone per day) with or without additional immunosuppression for remission maintenance. The scenario could include provision of a second 3 to 6 months course of Tocilizumab therapy in case of a further relapse.

Our current position on management of relapsing or refractory GCA requires further evidence base. We recommend a research agenda directed at efficacious and safe treatment of this particularly difficult sub-group, with careful documentation of GC toxicities. This may need to include randomised controlled trials of promising c-DMARDs either to induce or maintain remission in GCA.

Disclosures

[redacted]

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Tocilizumab for treating giant cell arteritis [ID1051]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**The Royal College of Ophthalmologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None from the tobacco industry.**
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this preliminary recommendation has not fully taken into account the current difficulty in managing those with severe relapsing and refractory Giant Cell Arteritis, particularly in those with extensive disease such as ischaemic complications and large vessel Giant Cell Arteritis.
2	We are concerned that this preliminary recommendation has not fully taken into account those who are diagnosed with Giant Cell Arteritis and have multiple co-morbid conditions such as Diabetes Mellitus, Osteopenia, Osteoporosis, Cardiovascular diseases and Glaucoma where treating with high dose glucocorticoids can be problematic and compound their existing premorbid conditions.
3	We are concerned that this preliminary recommendation has not fully taken into account those who are diagnosed with Giant Cell Arteritis who through the course of their disease have multiple-flares and are therefore at higher risk of an excessive cumulative glucocorticoid dose.
3	The breath of glucocorticoid toxicity is well documented in the literature. However, we are concerned that the economic modelling for the types of steroid induced

	adverse events may not be totally accounted for in the models here as they have not delineated those with refractory or relapsing disease who will have a higher cumulative glucocorticoid dose, than uncomplicated Giant Cell Arteritis. In the literature, the direct health care economic burden of complications induced by glucocorticoid use are excessive and in 2009 were estimated by *Mason SC et al* as at least an extra £84.2 million per year to the NHS. The majority listed below have profound health implications for the patient as well as the National Health Service: 1. Increase in weight and body mass index – obesity 2. Low mood, depression and depressive symptoms 3. Bone health – osteoporosis and fractures 4. Gastrointestinal – gastric ulcers 5. Ophthalmic complications – cataracts, ocular hypertension and glaucoma 6. Cardiovascular events- Hypertension and increased risk of myocardial infarction 7. Cerebrovascular events- increased risk of stroke and vascular dementia.
4	This preliminary recommendation has not been able to capture the increased direct health care costs of refractory disease; relapsing disease; manging co-morbidities and glucocorticoid toxicity or adverse events in Giant Cell Arteritis. Including increased admitted patient care, out-patient care, primary care and emergency care; surgery, in some; and increased length of stay in hospital.
5	We are concerned that this preliminary recommendation has not fully taken into account the patient voice from this disease group. Other vasculitic conditions have targeted treatments, and patients may not understand why they will not be afforded targeted therapy when the evidence exists that Tocilizumab has a cleaner safety profile than glucocorticoids, and has class 1 evidence (The GiACTA trial) that interleukin-6 inhibition is effective in treating Giant Cell Arteritis.
6	We are concerned that this preliminary recommendation has not fully taken into account the patient voice from this disease group regarding their quality of life and their independence. Glucocorticoid adverse events have a negative effect on quality of life and independence.
7	We are concerned that this preliminary recommendation could be seen as discriminating against those who are of older age. Giant Cell Arteritis has an increasing incidence with age and age may be a reason why, to date, there has been little quality clinical data. Older patients have a higher need of targeted therapy, as they have accumulated a higher number of co-morbidities. Completely rejecting a targeted treatment for any sub-type of Giant Cell Arteritis could be seen to discriminate based on age.

Insert extra rows as needed

From: [redacted]
CHAIRMAN: VASCULITIS UK.
[redacted]
Tel. [redacted]
Email: [redacted]

5th January 2018

NICE Appraisal Committee
City Tower, Crown Plaza.
Manchester.

Dear Sirs,

Tocilizumab for treating GCA

I attended the initial STA meeting in November as a Patient Expert and was disappointed with the evidence submitted by the manufacturer and felt the clinical and subjective patient evidence lacked strength.

Since the STA I have been seriously ill, so personally unable to coordinate a submission on behalf of Vasculitis UK to this second review meeting. I don't want to waste Committee members' time with unnecessary verbiage. I have no original or new data to contribute. However I have studied the BSR's well substantiated and detailed technical submission and Professor Ann Morgan's excellent submission, made from the viewpoint of a clinician with extensive experience in treating GCA.

Glucocorticoid toxicity has been long recognised as *the* major hazard in the treatment of all types of vasculitis and in recent years has been well addressed in small/medium vessel vasculitis through the use of steroid-sparing immune supressing medication, which permits reduction of glucocorticoids to low levels. However, adjunctive use of these immune suppressing drugs has proved to be largely ineffective in large vessel vasculitis. Thus there is a serious need for a suitable new drug and Tocilizumab *seems* to fit that need.

We (Vasculitis UK) do recognise that whilst the evidence for routine use of Tocilizumab in GCA may be still lacking in strength of evidence and that, as presented at the STA meeting, the cost is high. However, there is a strong case for use of Tocilizumab in refractory cases, those who have experienced serious side-effects of long term high dose glucocorticoids and those who have been subjected to excessive cumulative dosage of GCs. The BSR offers very good evidence of cost effectiveness in terms of potential cost savings.

Professor Morgan has highlighted the work of the new TARGET partnership and the accumulating data available through the UKIVAS partnership and other sources and the development of new algorithms. She raised the interesting concept of a future collaborative relationship between clinicians, researchers and NICE with a view to ensuring that NICE has early access to the data it needs for its decisions.

Thus, realistically and at present, we at Vasculitis UK would be happy were NICE to approve the use of Tocilizumab in selected sub-groups where it is going to be cost effective, of great clinical benefit and with substantial QoL benefit for patients. By the time of the customary review, in two years, there should be an ample body of new and better evidence to consider extending this use.

[redacted] – for Vasculitis UK.

[redacted]

Polymyalgia Rheumatica & Giant Cell Arteritis UK

The committee recognises the point that Clinical trial results show that after having tocilizumab plus corticosteroids for 1 year, more people are able to sustain a remission and manage on lower doses of corticosteroids compared with people having corticosteroids alone. We feel that insufficient consideration has been given to the fact that glucocorticosteroids work by 'damping down' symptoms systemically, whereas TCZ operates directly on the interleukin IL-6 which is a major agent in the disease. By doing so, it is directly treating the disease, which can accelerate recovery, and which explains why rates of relapse are reduced. Therefore, the assumption that TCZ is likely to be used for as long as steroid medication by itself is erroneous. It is more likely that patients will be able to reduce their overall levels of medication and be able to come off medication completely after two years. Currently patients are told that they will be on steroids for two years, but the reality is that this period is generally much longer. This is because steroids do not treat the disease itself. Therefore we would consider it reasonable to prescribe TCZ for patients who have refractory disease in order for them to have a chance to reduce their dependency on prednisolone. If that dependency is not reduced within a year it would be reasonable to assume that TCZ is not working, in which case it would need to be withdrawn.

As evidence we cite the 2012 study by Unizony et al, "Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica" .Arthritis Care Res (Hoboken). 2012 Nov;64(11):1720-9. doi: 10.1002/acr.21750. This study evidenced the clinical effects of TCZ in a group of refractory patients: "The mean followup time of this cohort since diagnosis was 27 months (range 16-60 months). The patients were treated with TCZ for a mean period of 7.8 months (range 4-12 months). Before TCZ therapy, the patients experienced an average of 2.4 flares/year. All patients entered and maintained clinical remission during TCZ therapy. The mean daily prednisone dosages before and after TCZ initiation were 20.8 mg/day (range 7-34.3 mg/day) and 4.1 mg/day (range 0-10.7 mg/day), respectively (P = 0.0001). The mean erythrocyte sedimentation rate declined from 41.5 mm/hour (range 11-68 mm/hour) to 7 mm/hour (range 2.2-11.3 mm/hour; P = 0.0001)."

In the consultation document, the committee emphasises several times the age demographic of the population with GCA. A misleading impression is given that 'most people with GCA' are in their 80s, although the average age of onset is given as 73. This is illogical, and fails to recognise that there are many people with GCA in their 60s and even in their 50s. When referring to the likelihood of co-morbidities, our representative did mention that many people with GCA are elderly, but certainly did not say that 'most people are in their 80s". We therefore consider that the assumptions of the committee regarding age range and the calculations regarding QALYs may be skewed and request that these figures are revisited.

Subsequent to the point made above, it is also important to note that in August 2016, NICE published its policy on the use of tocilizumab to treat Takiyasu Arteritis,

https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/08/clinical-com-pol-16056p.pdf.

A close reading of this document reveals the extent to which Giant Cell Arteritis and Takiyasu's Arteritis are similar, with the exception that TA attacks a younger age group. We note that before the approval of TCZ for Takiyasu's, there was the possibility of treating refractory GCA with other immunosuppressants. However, TCZ was approved for TA, citing evidence from previous studies which included patients with GCA. We quote from page 10 of NICE's clinical commissioning policy on TCZ for TA:

The highest level evidence for clinical effectiveness of tocilizumab was from a systematic review and meta-analysis by Osman et al (2014) investigating the role of biological agents in the management of large vessel vasculitis. Out of a total of 25 studies shortlisted, 5 case series with 19 total GCA patients and 4 case series with a total of 11 TAK patients were specific to tocilizumab. There were only 3 RCTs and none of which involved tocilizumab. In the meta-analysis, all 19 GCA patients treated with tocilizumab achieved disease remission. There was CS dose reduction for all patients and total discontinuation of steroids in 9 (47%) patients. Pooled mean CS dose reduction was 16.55 mg per day (95% CI -26.24 to -6.86).

As the national (UK-wide) patient organisation representing GCA patients in England, we respectfully request the committee to consider this apparent anomaly of a drug being approved for one set of patients and failing to be approved for another set of patients with a very similar disease (both forms of large vessel vasculitis, both characterised by over-production of IL-6). This even though the evidence cited in the TA commissioning policy cites evidence about the efficacy of TCZ for GCA. We do suggest that there may be an equality issue for the committee to consider here.

Our final point is that the committee document states that there has been no adequate new treatment for GCA for 'several years'. The fact is that prednisolone was first approved for clinical use in 1955. There has been no significant advance in treatment of GCA for over 60 years, which is longer than the lifetime of some of our members.

Thank you for your consideration.

[redacted]

[redacted]
Patient Organisation Worker

Polymyalgia Rheumatica & Giant Cell Arteritis UK

I am in support of approval for use of Tocilizumab in certain circumstances to be used for treatment of GCA.

In organising the Support Group I have had contact with many members and the majority of them who suffer with GCA have been on glucocorticoids for in excess of 5 years, some in excess of 10 years, having been yo-yoing dosage with relapses during this time.

The side effects can be so serious where people have developed osteoporosis and the danger of stroke or aneurysm is worrying.

Although an average date of onset might be 70 there are members of our group, the largest in UK, who are still of working age in their 50s and 60s. They find it difficult to work and have to have periods off work to cope.

I URGE YOU TO RECONSIDER APPROVING THE USE OF TOCILIZUMAB FOR THE TREATMENT OF GCA IN SELECTED CASES.

[redacted]

[redacted]- Support East Anglia

Tocilizumab for treating giant cell arteritis [ID1051]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 4 January 2018 **email:** tacommc@nice.org.uk or NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Justin Mason
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**JC Mason has participated in medical advisory meetings for Roche**]
Name of commentator person completing form:	[Justin Mason (Imperial College) Clinical Expert nominated by Roche]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Overall I found the report accurate and well-balanced. Thank you for the opportunity to comments I have a few points to raise:
2	Although I take on board the excellent modelling work done, my immediate response to the cost-effectiveness estimate for tocilizumab of at least £65,800 per QALY is why this is so much higher than for the same drug for rheumatoid arthritis. Although I fully accept I have no skills in financial modelling, the QALY makes me concerned regarding whether we have modelled its use in GCA correctly? I accept this is very difficult indeed but I think this requires further consideration in any future appraisals.
3	The report conveys the impression that GCA is a disease that needs new drug therapy, and that GCA patients represent a group at major risk of serious steroid side-effects. The main reason for decline at this stage is the cost. However, I think the importance of the steroid-sparing effect of tocilizumab (shown in the Stone et al paper NEJM 2017) has been somewhat over-looked in the report and needs further consideration. We know it is the cumulative dose of steroids that is most closely related to side-effects and the use of tocilizumab is likely to reduce this impact.
4	The opinions obtained from experts and organisations including the BSR prior to the meeting recommended targeting of tocilizumab to high risk patients (pre-existing diabetes, CV disease, hypertension, osteoporosis etc) and to those with refractory disease. This is in contrast to prescribing the drug in all cases which was put forward to the Appraisal Meeting. In my opinion targeting to high risk groups is the way forward for the introduction of this important drug.

5	One important aspect to consider looking forward is that if we 'lose' tocilizumab for the NHS over the next year or two, the impact on the provision of new treatments for GCA in the UK could be very serious. Such a decision might significantly impact future clinical trials or research in this area, in which no therapeutic progress has been made for more than 50 years. This reinforces the need to look for a more affordable use of tocilizumab in GCA.
6	The duration of treatment in this disease is extraordinarily difficult to predict or model. I don't think the statement that 'tocilizumab treatment is likely to exceed 2 years' strictly reflects discussion at the meeting or input from experts prior to the meeting. The most widely held view was that treatment would typically be for 18-24 months. Although some may exceed two years, my own opinion is that this would be relatively small – maybe 10-15 %. Furthermore, as the GiActa trial showed a significant benefit following one year of therapy, I think most rheumatologists would accept a limit of one year's therapy if this was the only way in which the drug can be introduced within the understandable economic restrictions we all have to work within.

Insert extra rows as needed

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was diagnosed with GCA in October 2015. This was possibly due to my wife being diagnosed with lung cancer and the subsequent surgery. I was given steroids (40mg) immediately and gradually reduced by February 2017 to 7mg. At this time I was feeling absolutely terrible with aches and pains all over my body. However, my Rheumatologist and GP kept telling me I had to get off steroids and they said take plenty of painkillers but keep reducing the steroids. I was eventually diagnosed with PMR and the steroid dose increase again. Initially this gave me some relief from pain but, once again, the Rheumatologist and GP said I had to reduce the steroid dose as quickly as possible. I adhered to their plan and for the next 8 months I began to really suffer greatly - often not being able to get out of bed. Just to have some quality of life I had to take maxi,mum doses of painkillers to keep going. I eventually discovered the PMRGCAuk website (in November this year) and their excellent Forum, and found that the only way to try and get off steroids was to take a very slowly, slowly approach when developing a "taper plan". I consulted my Rheumatologist and suggested that I increased my steroid dose to 20mg and then taper very slowly. She was not very convinced by my suggestion and kept pointing out the side affects of steroids. Anyway, I'm sticking to my plan and so far feel good and my quality of life has returned. However, I feel that I spent well over a year really suffering (maybe at the age of 81 you might say well "what does the old bugger expect!!) but, I've paid my taxes and contributed to the UK prosperity over the years (in fact, I still have a part-time job) so why should oldies like me not benefit from a treatment which might benefit us in our "so called" old age. I feel that any treatment which will help GCA (and PMR) patients reduce their steroid dose in a reasonable time frame - with a "quality of life" - will benefit us all. Also, when you look at the cost of consultations with consultants and GPs over the last couple of years, perhaps the treatment with this new drug would have reduced these cost significantly and, MORE IMPORTANTLY, have reduced the suffering of patients. In hindsight, I not saying that if Tocilizumab had been available 2 years ago that I would now be off steroids but I am saying that if this treatment was available on the NHS now , it could reduce the suffering of patients (mainly oldies). Lets face it, we suffer enough in this day and age!!! Come on, licence the treatment - NOW!!

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Page 6 'Most of the patients are aged over 80 years' I contracted Giant Cell Arteritis when I was 60. Are older patients to be denied a decent 'quality of life' because of their age? I have had GCA for 7 years and have suffered 4 relapses in that time. I have suffered blurred vision, excruciating headaches, fatigue, bleeding skin, hypertension, weight gain due to high doses of steroid. This is an extremely debilitating disease. I also take Methotrexate weekly to try to help to reduce the steroids. Tocilizumab is the first drug in nearly 50 years to be shown to be effective for GCA patients and I would definitely welcome the opportunity to take it as my Rheumatologist believes it would help me. I hope sincerely that Nice will reconsider its position on this for 'refractory' patients in the first instance. Disclosure - No, to feel 'normal' again would suffice.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a sufferer of GCA for the past three years I was disappointed to see TCZ rejected, primarily on cost grounds. Your costs calculations are not shown. From my experience it is not just the cost of drugs, the following should have been costed (including NHS staff time, clinical and facilities usage) and included in the assessment: 1. Monthly blood tests 2. Monthly GP consultations 3. Rheumatology appointments 4. Haematology appointments 5. Dexascans 6. Other prescribed drugs: Lansoprazole, Calceos, Statins (as steroids raise the cholesterol level), various sleeping pills 7. Emergency treatment. A GCA flare up earlier this year gave me an abscess requiring an emergency in patient operation. What cost that? I take exception to the age range used in your conclusions. Certainly over 50 seems to be the norm, but not into the 70s. Mine started in my 60s; I know of others in a similar age range. I started on 50mgs of red, have been down to 6mgs and all stations in between, depending on the extent of flare ups. All an additional cost to the NHS, regardless of the quality (or lack) of my life. At this rate, which no further flare ps I'll be free from pred in just over two years. In the meantime the cost to the NHS continues. I estimate that I shall have consumed Â£6,000 worth of GP time alone. I ask myself the question: how can the USA and Canada give the nod to TCZ whereas we cannot? Do they value life more preciously? Cost maybe a factor, but not a finality.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Retired social worker
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a patient with GCA and PMR, diagnosed at aged 70, 7 months ago, and currently prescribed Prednisolone I would just like to make a few comments. As Tocilizumab is approved for use in USA and Canada I cannot see why it cannot be approved by NHS England. As a patient I can confirm that this is a very debilitating illness that drastically effects a sufferers life in many aspects - the pain, fatigue and general ill health and effects of Predisolone are hard to bear at times. Patients also experience flare-ups whilst reducing steroids as I am at present and I understand that this drug has been proved to assist the reducing process of steroids. I understand from the document that cost seems to be the major consideration in not approving this new drug and I would ask that NICE consider the impact that this news has on patients. It feels to me that because PMR and GCA are mainly diseases of the elderly that we are being marginalised and discriminated against. PLEASE RECONSIDER YOUR DECISION.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Retired nurse
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I m commenting to ask you to reconsider your status on Tocilizumab for treating Giant Cell Arteritis. I am almost 3 years into this awful disease and am still on 10mg of prednisolone. I have been on a 'yoyo' dose since the beginning and it is sometimes soul destroying. You think you are never going to recover so if there is a treatment out there which has possibilities for improving quality of life then surely it should be given more consideration. I am not as old as the paper suggested and neither are many sufferers. I am 65 years old now so started with this disease when I was 62. I am unable to take Azathioprine due to a rapid and dangerous increase in liver enzymes and I cannot take Methotrexate due to severe side effects. I know I am not alone in this. So I have to just go up and down on the prednisolone. My rheumatologist told me this could last 2 years, possibly less!! A joke, GCA commonly lasts longer than that. I would just like the committee to reconsider the use of Tocilizumab for this disease. Not necessarily for everyone but with feasible criteria. Thank you for reading.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was 68 when GCA was diagnosed. The long term effects of preds is a considerable concern and the decision to refuse Tocilizumab doesn't take proper account of the age profile of GCA and the additional costs associated with further conditions, which could be reduced with Tocilizumab

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Researcher
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I, and those i know with gca, mostly experienced onset in 60s or early 70s. Ive been on steroids for 4 yrs,, now on methotrexate and am 78. If i had had access to toxilizumab, i might have been drug-free by now. And average LE for women is 83. It is therefore worth using this drug in terms of QALYs . I urge NICE to reconsider thectefusal of the new drug which is successful in other countries. I was lucky to avoid blindness, having had optical incidents before i was diagnosed, sever al months after onset of other symptoms of pmr. Treatment has allowed me to continue working part time as well as volunteering and supporting my descendants in various ways. Please dont write off people aged over 70! Side effects of steroids are well known. Methotrexate side effects on liver and kidney rather less so. If the new drug has less harmful side effects and doesnt require so much monitoring by blood tests,this would save money for bhs.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I wish to take this opportunity to object in the strongest terms to the decision by NICE not to recommend Tocilizumab (TCZ) for use in treating patients with Giant Cell Arteritis (GCA) on the grounds of funding. I was diagnosed with Polymyalgia Rheumatica and Giant Cell Arteritis in July 2015 at the age of 60, following a month's long illness. I was treated with high dose Prednisolone to control the symptoms and reduced to 25% of my initial dose within 6 months, but this dosage has been very difficult to maintain due to flares lasting up to 2 months each time. I have recently, and very reluctantly, agreed to take Methotrexate (another extremely toxic medication) as I was struggling to reduce the steroid dosage. I requested TCZ but this was refused by my Rheumatologist, no doubt a directive by the NHS on the grounds of cost. TCZ is the first major breakthrough in many decades that is proving, so far, to be very effective in the treatment of Giant Cell Arteritis with particular emphasis on shortening the duration of the illness and, ultimately, the overall long term cost to the NHS to treat many associated medical conditions from long term use of steroids. In the NICE Appraisal consultation document it is quoted in Recommendations "Why the committee made these recommendations" it has been noted that "High doses of corticosteroids may cause skin problems and weight gain, and long term use can lead to diabetes and osteoporosis" No mention whatsoever that long term steroid use is likely to cause Opthalmic complications such as glaucoma and cataracts. Neither is there any reference to GCA patients having a 17 fold risk of thoracic aneurysm and a 2.4 fold risk of an abdominal aneurysm. There is also no mention that there is a risk of mortality caused by a fatal myocardial infarction, fatal stroke and thromboembolic events. The summary document therefore fails to interpret and/or provide all of the medical information for consideration! On the grounds of refusing recommendation to fund TCZ for the treatment of GCA, from the information provided within the supporting documentation, there are 220 patients with GCA for each one million residents in the UK, which is a minute proportion of people to be funded for this treatment within the NHS. This factor should have been an overriding consideration in reaching the decision to fund TCZ for the treatment of GCA! Costings to fund TCZ are, from the supporting documentation, difficult to determine as in many cases the figures have been redacted on the document! The Appraisal consultation document has not, therefore, complied in this respect! Setting aside the cost implications, it is the very fact that patients do and will suffer agonisingly poor health for much longer than may be

	necessary. Long term physical health invariably, and understandably, causes mental health issues adding even more cost to the NHS. This is neither fair or right! In noting that this decision will be reviewed again by NICE in 3 years, there will be many fellow sufferers of GCA who will be deceased and so, on that basis, the NHS will have failed us in the short and both the long term. This decision does not, in my opinion, deliver the duty of care promised by the NHS to one of the most vulnerable and enduring sectors of society! There is, in my opinion, an ageism factor to be considered here. I have submitted these comments from the point of view as a sufferer of GCA. For almost 3 years I have endured physical and mental pain every single day, I currently cannot live the healthy and active life that I once had! I contracted GCA through no fault of my own and despite a healthy lifestyle. It is both frustrating and disappointing that a cure for this condition has not been found largely, it seems ironically, because the pharmaceutical companies will only develop medicines for which there is maximum financial gain. I therefore wholey support this decision being overturned.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Retired
Other role	
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My wife 86 has suffered from PMR for over 12 years, has tried many times to drop steroids,with out success, any hope of relief would be a godsend. Why develope a drug aimed at a condition that is most prevalent amongst the over 70's if you are not prepared to sanction it on age grounds. In this day & age of political correctness what a disgrace , this appears to be age discrimination. We are astounded that so little is known about this cruel condition, most Doctors & rheumatoid Specialists seem to know so little. Is it not about time that something was done to encourage researchers to develope treatment for PMR, at the same time this could lead to unknown progress in other areas of inflammatory conditions, saving the NHS billions in the future, who knows this surly is the sort research catalyst that medical science relies upon to progress.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was diagnosed with G.C.A. aged 52. It has had a huge impact on my life. I have yoyooed from 60-10 mg Prednisoloneover this time also on Mychophenalate. I have had gluacoma, cataracts, steroid induced diabetes, recurrant infections, muscle weakness and weight gain. I am self employed so I can choose working hours due to fatigue but have a reduced income. This illness has a major effect on lives, your stats suggest it is only retired people who get this illness, please reconsider for those of working age.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have read all of the project documents and, as a patient diagnosed with polymyalgia rheumatica (PMR) and large vessel giant cell arteritis (GCA), I would like to contribute my experience for your consideration in evaluating Tocilizumab (TCZ) as an approved treatment for GCA. I was diagnosed with PMR in 2008 aged 62 following a lengthy flu-like illness. I developed pain and debilitating stiffness in my neck, collar bones, shoulders and lower limbs, with difficulty getting out of bed, getting up off the sofa and having to walk down stairs one at a time. I tired easily and became increasingly anxious and depressed at my situation. My then GP immediately put me on 20 mg of Prednisolone and within 5 days I felt amazing, totally pain-free and fully mobile. I have subsequently had numerous unsuccessful attempts to wean off the steroids and the symptoms always returned when my steroid dose fell below 12 mg. In February 2011 I was put on Methotrexate, which was ineffective and my hair fell out. My PMR symptoms continued to reappear with the same severity on steroid doses less than 12 mg.Â In 2013 my eyesight became cloudy and I was unable to drive; I was diagnosed with progressive cataracts in both eyes, likely due to steroid medication, and had successful surgery to repair both eyes. I have also suffered muscle loss and ligament damage that has permanently impaired movement in my left shoulder, again likely due to steroid usage. In December 2014 I was started on Azathioprine, which made me extremely nauseous (requiring medication) and was also ineffective. From that point onwards I have endured persistent urinary tract infections requiring lengthy antibiotic treatment to this day.Â After weaning off Azathioprine and steroids in 2016 with a view to obtaining a new medical opinion at baseline, I was once more in severe pain with the familiar stiffness in my neck, collar bones, shoulders and lower limbs to the extent I had to be massaged before I could get out of bed and had difficulty walking down stairs. At this point we decided to seek a private specialist consultation who recommended a PET-CT scan, which we paid for privately. The scan revealed not only active PMR but also an aortic aneurysm.Â A subsequent ultrasound scan revealed avid large vessel GCA with halos in both common temporal arteries and arterial thickening on the left and the right, hitherto undiagnosed in primary care. The consultant also noted my tearful presentation and low mood caused by despair at my ongoing symptoms. I was then recruited to the SIRRESTA clinical trial of an anti-IL-6 biologic agent, GSK's Sirukumab. I entered the double-blind randomised trial in August 2016 of bi-weekly subcutaneous injections accompanied by a blinded tapering steroid dose starting at 20 mg. The improvement was immediate and total and I felt back to my old self; this continued to be the case on the blinded first year of the trial until I flared at week 48 of the trial in July of this year and went on to

	15 mg of open-label steroid. At the beginning of August 2017 I progressed to the open-label phase of bi-weekly Sirukumab subcutaneous injections and was able to quickly taper steroids to currently 3 mg daily with no breakthrough symptoms whatsoever. I have never been able to get down to this level of steroid dosage without breakthrough symptoms since my original PMR diagnosis. A recent ultrasound confirmed remission of my GCA and my aortic aneurysm is unchanged in appearance. Unfortunately, Glaxo terminated the SIRRESTA clinical trial on commercial grounds in October and my last Sirukumab injection was given on 10th October. At time of writing (December 2017) I am still on only 3 mg of Prednisolone with no breakthrough symptoms so far. My consultant believes that TCZ is sufficiently similar in mode of action for me to continue my remission from what could have been a devastating outcome had I become blind, or worse if my aneurysm had progressed unchecked. I cannot emphasise strongly enough how awful has been my experience of the symptoms of untreated PMR and large vessel GCA. To date I have consumed more than 31,000 mg of steroids in the 9 years since my initial PMR diagnosis and I feel that I have already paid a price in terms of sight defects and muscle wastage, with the potential for further problems and loss of quality of life if I become dependant upon steroids as I grow older without access to effective steroid-sparing treatments, particularly as I appear to have been well-served by an anti-IL6 agent. I note that in the project documents the reported mean age of patients with GCA is rather fluid: The ERG notes that there is an important difference in the mean age of patients in the GiACTA trial (69.05 years) and the mean age of patients in 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. (ERG Cost Effectiveness conclusions section 5.3) In NICE's Recommendations document, this somehow transforms into: They (the patient experts) highlighted that because the disease is most common in people over 80 years old, these side effects are often in addition to existing health problems. (Section 3.1) It is my 'real world' experience that whilst I was 70 when my GCA was diagnosed, this was something of a chance finding and already well established. During the past nine years I have moved house several times and have been treated in three different primary care trusts for PMR; for the first eight years there was no attempt to screen for GCA in primary care and I fear it would have continued unchecked if I had not paid for a private scan. This leads me to believe that age of onset is often significantly earlier than age at diagnosis, in part due to inconsistent approaches to testing for GCA in the presence of other vasculitic conditions; a task that becomes more difficult if high-dose steroid treatment has already commenced. This point is not made anywhere in the documents. The outcome of your consultation has great bearing on my own future prospects, as it will have on the prospects of all patients in my situation. I hope that my experience will contribute to your collective understanding of the 'real world' impact of your recommendations. Thank you very much for the opportunity to comment.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am 75 and I have GCA. The side effects of steroids, which I have been taking for 14 months, are debilitating and life changing. Tocilizumab has been approved for Takiyasu's Arteritis. This is very similar to GCA which was referred to as evidence with GCA patients. Tocilizumab targets the cause of the symptoms rather than just the symptoms. It is the first specific new treatment for GCA in more than 60 years.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am 66 years old and fell ill with GCA and PMR in April 2017. I was diagnosed at the end of July. I find it very regrettable that NICE has decided not to license tocilizumab for treating GCA. In my case I cannot reduce prednisolone below 25 mg per day without experiencing a flare in GCA symptoms. I am now on 40 mg per day plus a weekly dose of methotrexate. I would very much welcome the chance to try a medication that would tackle the root cause of the illness rather than simply dealing with the symptoms. My way of life has become very restricted because of my conditions and the side effects of prednisolone result in further restrictions. It seems particularly hard when I understand that NICE has licensed tocilizumab for another similar condition, Takiyasu's Arteritis, using evidence from a trial with GCA patients. I hope you will reconsider your decision in view of the benefits that GCA patients would gain from the use of tocilizumab.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I comment as one who has Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica who has had two GCA 'flares' in the past six months while trying to taper the dose of Prednisolone from 17.5mg/day to 15mg. I started on 60mg in February 2016, so the 'expected' two years on Predmisolone is unlikely to happen and I suspect that it will be years before remission. I was 61 years old when diagnosed, so not one of the 'over 80s' mentioned in the document. The fact is that this condition normally affects people over 50, many of whom have decades of life to come. I believe that, since the plan would be to use this new drug only on people with GCA who are having trouble reducing the dose of Prednisolone because of flares, and the fact that the illness is relatively rare, the cost would not be too great a burden on the NHS. That the new drug would improve the quality of life for sufferers currently in their 50s, 60s and 70s is surely worth the cost.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a 67 year old female who was diagnosed with PMR three years ago. After one year I subsequently developed GCA. I would firstly like to respectfully point out that from the evidence of two websites that I frequent GCA affects many patients that are in the 50-60s age group (sometimes younger) Many of these patients, like myself, were active; many of them employed in caring professions or like myself took early retirement but we're still involved in many charitable, voluntary organisations to benefit the community as a whole. I therefore feel that many of us, as patients, have many more years to contribute and be involved in society and although the age is stated 50-60s on the can, we do not look that age, act that age and had felt well until the onset of GCA/PMR. From my own personal experience, the experience of GCA has involved a very prolonged treatment plan. The PMR is manageable but because of severe head pains with the GCA this has necessitated me being at a much higher dose of steroids to control this inflammation for a prolonged period of time. I have no idea how long I can continue a very slow taper of the steroids before the inflammation breaks through and the steroids do not control the pain and inflammation. There is no light at the end of the tunnel, no definitive time for recovery, with the possibility of a very long recovery time with many possible relapses anticipated as the steroids do not deal directly with the cause but just mask the effects. This in itself , from a psychological point of view poses its own problems: a prolonged treatment plan, with no assurance of cure, a possibility of flares and having to increase the level of steroids to control the inflammation, thus adding to the game of snakes and ladders. The emotional repercussions of this are great, adding to stress, which in turn necessitates more steroids to control the pain and so the wheel continues. With the introduction of TCZ this would give real hope, less eventual pressure on GPs and Consultants. As TCZ operates directly on IL-6 I believe this would accelerate recovery, relapses would be reduced and consequently less time would be spent on a TCZ and steroids regime. I have read with interest and I admit envy the experience of my American counterparts, on several forums that I have access to. These American counterparts, who having started on their regime of TCZ and steroids, often after me, have now nearly finished their journey of treatment whereas I still feel very much at the beginning of mine and still counting. I really do feel that the emotional and psychological aspect of a non - treatment plan but control plan (I.e steroids) for GCA should be taken into account in this submission for approval of TCZ. The above approach (I.e steroids alone) can be quite distressing, unmotivational , depressing, and relentless, adding to the stress and longevity of the GCA condition unnecessarily .

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a sufferer of GCA, I am bitterly disappointed that NICE has rejected the approval of TCZ for use of this condition. I am otherwise healthy but have serious concerns about taking high levels of steroids to control the GCA, knowing that they are probably developing numerous other health conditions. These will cost the NHS dearly. My quality of life is threatened by the long periods of high doses of steroids. I contribute a lot to society, through volunteering and family support and know that if I lose my sight or deteriorate because of diabetes, etc., I will become a very 'expensive patient.' Surely TCZ could be approved and used discretionally according to an individual's state of health, quality of life and contribution to community. I urge NICE not to make assumptions about GCA sufferers and to seriously reconsider its decision. There are very many people like me who wish to continue living a fully functioning, valuable life for may years to come.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional - CNS Rheumatology
Other role	[redacted]
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	3rd January 2018 - Response to NICE Consultation for Tocilizumab in Giant Cell Arteritis In practice, patients with PMR/GCA/LVV who have refractory or relapsing disease require long term higher dose Corticosteroids. They have more frequent Outpatient appointments, there are more telephone consultations in between appointments due to flares in the condition and increased stress and anxiety for the patient who are extremely fearful of sight loss, the consequence of a Vasulitis flare and the impact of long term high dose steroid therapy. Patients have no alternative but to take high dose steroids as there are no effective substitutes. Research clearly shows that there are only a proportion of patients who have sustained remission on steroids alone. Therefore all patients specially the younger Age 50 + are highly likely to develop side effects of steroid therapy which will have a long term impact on their physical and mental health and their ability to work, which in turn will have a financial impact on the economy. From a Clinical Nurse Specialist perspective, a large proportion of my Consultation is to address the patient's comorbidities including Osteoporosis, Cataracts, Diabetes, weight gain with an impact on Osteoarthritis, effect on sleep, fatigue, low mood and depression. Increasing steroid therapy due to relapsing or refractory symptoms is extremely stressful for the patient, leading to more anxiety and less confidence in the treatment and more dependence on high dose treatment. Patients who are individually chosen to receive Tocilizumab will be monitored closely for their response and the ability to reduce the prednisolone dose to a safer level. Alternative treatments for this potentially devastating disease will have a lasting, positive effect on the treatment of Relapsing, Refractory cases. In turn, the course of the condition will be managed more effectively with cost-effective implications.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Rheumatologist
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There is an unmet need for patients with refractory and relapsing GCA. A proportion of patients need on-going glucocorticoid treatment in relatively high doses and for prolonged time, despite the use of steroid sparing agents, to control their disease. This results in significant morbidity considering the age of this group of patient, therefore the availability of Tocilizumab as a treatment option for this group would be welcome and should be cost effective.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	NICE assume that most people with GCA are in their 80's, I was diagnosed 8 years ago at the age of 63. I have had the burden for the first two years after my diagnosis of high doses of steroids as after each reduction below 20mg my symptoms reactivated. I progressed from taking one medication to at one point 4 different types to try to control my high blood pressure and have been on 3 types for the last 5 years. I also had to take Alendronic acid plus Adcal to reduce the risk of osteoporosis, both medications I would not have had to take if not on steroids. I was put on Mycophenolate by my hospital consultant after two years old steroids with frequent reactivation and have since been able to reduce the steroids to 2.5 mg.as TCZ targets the cause not just the symptoms of GCA I would have like the opportunity to take this drug. The immunosuppressant drugs I take make me vulnerable to any infections that I have leaving me weak and fatigued for weeks at a time.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We as a group were most concerned to hear that you are not going to approve the use of Tocilizumab for treating giant cell arteritis. In answer to your questions:- Has all the relevant evidence been taken into account? - No. Severe, relaxing and refractory GCA only responds to GC when long term high doses are maintained and with its associated major toxicity together with increased likelihood of cardio vascular events, obesity, diabetes etc. Relaxing and refractory GCA groups are in desperate need of additional treatment options Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? - Assumptions are made that GC are tapered to zero in all cases of GCA, this is not the case as patients are often maintained on a low dose along with DMARD therapy. The cost of treatment with Tocilizumab of these groups would be much lower. Are the recommendations sound and a suitable basis for guidance to the NHS? Tapering GC alone is not effective for relaxing and non responding groups, therefore not recommending Tocilizumab for these difficult to treat groups leaves an unmet need for treatment. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes - Age discrimination may be a concern as GCA mainly affects 50 plus age group. With state pension age fast approaching 70 this could mean a possible 20 year period of unemployment and subsequent financial hardship in addition to the stress of the disease itself. Due to time constraints I was only able to discuss this with the following members, who gave their full support to the above comments. Although I feel had we held a meeting to discuss the above comments everybody would have given their full support. [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Cons Rheumatologist
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We at [redacted], rheumatology department (Dr [redacted], Dr [redacted] and Dr [redacted], Consultant rheumatologists) support the BSR rheumatology response to NICE consultation for Tocilizumab in Giant Cell Arteritis

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Rheumatologist
Organisation	[redacted]
Location	England
Conflict	[redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I wholeheartedly support the British Society of Rheumatology Response to the NICE Consultation for Tocilizumab in Giant Cell Arteritis. For the reasons outlined in the BSR response, I would particularly value 12 months Tocilizumab in my relapsing / refractory patients and those with co-morbidities exacerbated by glucocorticoids such as osteoporosis, mood disturbance, HT and diabetes.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Rheumatologist
Organisation	
Location	England
Conflict	I have attended educational meetings with support received from multiple pharmaceutical companies, but no relevant disclosures
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have treated a patient with biopsy positive GCA and ischaemic complications with Tocilizumab. She is in her late 70s and was referred to me with a threatened right visual field after losing her vision in the left eye despite high doses of oral and parenteral steroids. I'm pleased that giving her Tocilizumab has certainly stabilised her condition and most importantly allowed me eventually to successfully wean down the steroid treatment. I look after many patients with GCA and I strongly believe that most of them will do well with a decreasing course of steroids over a period of 2 years, however; in a proportion of GCA patients that isn't possible without a significantly higher cumulative doses of steroids, which is associated with significant morbidities. I care about my patients as well as the best utilisation of the NHS resources, so I believe the correct use of Tocilizumab in GCA with be more cost effective in the long run, especially the duration of treatment is well defined in the majority of patients. If we take in consideration the costs associated with the steroids adverse effects and other co morbidities. I strongly urge you to allow us to offer this important treatment to those patients with refractory or large vessel GCA.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Retired University Administrator
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As someone who has experienced GCA, I would like to comment on the recent decision by NICE not to approve tocilizumab for the treatment of GCA. I find it disappointing that this biologic drug which treats the disease itself rather than just treating the symptoms - as is the case for corticosteroids - will not be available to clinicians as a treatment option, particularly for recalcitrant disease. I was diagnosed with GCA in December 2015 shortly before my 67th birthday and four months after retiring from full-time employment. I started treatment on prednisolone at a dose of 60mg per day and the relief of symptoms was almost immediate. My prednisolone dose was tapered to zero over a period of 85 weeks and in that time I had one relapse, with symptoms of polymyalgia rheumatica. I calculated my cumulative steroid dose to be 6.125g. I consider myself fortunate compared to many patients with GCA who experience several relapses, and consequently require treatment for longer periods of time with higher cumulative corticosteroid doses, sometimes in combination with steroid-sparing immunosuppressant drugs. My younger sister was one such patient. She was diagnosed with GCA at the age of 60 and was treated with prednisolone alone and then in combination with methotrexate until her death from a GCA-unrelated cause at the age of 65. I have read that GCA is the most common form of vasculitis. It is, however, a relatively uncommon disease with a low level of public awareness. For this reason it can be an isolating illness for patients. GCA sufferers can appear quite well to their friends and family, and changes in their condition are probably attributed to the normal ageing process rather than a systemic illness that can last for a long time. After completing prednisolone treatment, I was discharged by my rheumatologist to primary care. I assume I am in remission, which obviously I hope will be sustained. I have experienced some steroid side-effects and have been told that I have steroid deconditioning, which continues to have an impact on my ability to perform everyday activities. I have received some benefit from physiotherapy. However, I have an underlying anxiety that my aches and pains may signal a disease relapse. While GCA is an illness of older people, it is important to note that many GCA patients are diagnosed in their sixties and do not regard themselves as elderly: I, for one, certainly do not! Hopefully I will make a full recovery from the illness and have many years of active life ahead of me to be enjoyed with my family. Like many women in my age group, I have caring responsibilities, as my husband has significant health problems. I do not have the expertise to comment on the calculation of Quality Adjusted Life Years for the assessment of tocilizumab for GCA. The decision to deny approval of tocilizumab for GCA but giving approval for Takiyasu's Arteritis appears inconsistent to me. Furthermore, it is a decision that could be viewed as discriminating against GCA patients on the grounds of age.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Rheumatology ST7
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	1. Has all of the relevant evidence been taken into account? I agree with the British Society for Rheumatology (BSR) response to the statement: In the final recommendations, no clear distinction has been made between the different subsets of GCA. This is despite the consultation document referring to this accepted clinical delineation further on. It is widely accepted that GCA has different subsets; those with purely cranial disease, those with more widespread vascular involvement termed Large Vessel-GCA (LV-GCA), and those with glucocorticoid (GC) refractory and relapsing disease. It is these last 2 groups as well as in patients with co-morbidities or pre-existing adverse effects that may be exacerbated by GC, who are in desperate need of additional treatment options, who need to be considered for Tocilizumab treatment rather than the GCA cohort as a whole. The NICE consultation does not appreciate that the cumulative GC use in these subsets is greatly increased, resulting in significant clinical and economic burden.
Section 2 (The technology)	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I would argue that the summaries, as stated by the BSR response, do not take into account that GCA varies in severity. Severe and extensive GCA is unresponsive to GC unless they are maintained long term at doses associated with major toxicity. Severe and extensive GCA is also associated with a higher likelihood of ischaemic complications, vascular damage, including aortic dilatation, and cardiovascular events. Costs averted with efficacious therapy with Tocilizumab in this sub group are the costs of treating serious GC toxicity, vascular damage and cardiovascular/cerebrovascular events. Furthemore, as noted in the BSR response to this document, the summaries assume that GC are tapered in all cases of GCA to zero. This is not the normal rheumatological practice in treatment of other vasculitides and connective tissue diseases where patients are often maintained on low dose GC (< 5 mg daily) along with adjunctive conventional or biologic disease-modifying anti-Rheumatic Drug (c or bDMARD) therapy. Using this model patients with GCA may not require Tocilizumab treatment for greater than 12 months again significantly reducing the cost effectiveness estimate (details in formal BSR response).
Section 3 (The manufacturer's submission)	3. Are the recommendations a sound and suitable basis for guidance to the NHS? I would argue no. Some patients may be able to taper to zero with respect to glucocorticoid therapy. However in cases of LV-GCA and relapsing groups, who by very definition are refractory to GC, there is no proven role for cDMARDs as steroid sparing agents. By not recommending Tocilizumab for these difficult to treat subsets, NICE

	still leaves an unmet need for efficacious treatment. There are no current effective therapies available for these patients.
Section 4 (Consideration of the evidence)	4. Are there any aspects of the recommendations that need consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? As the BSR response argues, these recommendations may be construed to discriminate against older people and against people who currently have no choice but to take long term steroids for disease control. GCA is a disease of older people, typically affecting people from the age of 50 with a peak incidence some decades later. This is the only vasculitis that is almost exclusively treated with GC monotherapy, due to a lack of treatment alternatives. Age is almost certainly a factor in the historical paucity of clinical trials and high quality clinical data, yet older patients are in the greatest need of GC-sparing medications due to the high GC doses required and higher number of co-morbidities. As such, limiting treatment options could be seen to discriminate based on age. Additionally, although GCA predominantly affects older people, many patients with LV-GCA are younger and may still have over a decade left of their working life. Not giving these patients a reasonable treatment alternative is condemning them to a lifetime of significant disability and early unemployment.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am commenting as a patient with GCA who is approaching her 4th year on steroids. I understand that the condition once treated is in remission but never cured. Knowing that steroids have many side effects it would be of great advantage to have this alternative drug available. I have already had one flare and had to go back on a high dose of steroids. If I should have a further relapse I really do not want to go back on a very high dose of steroids again.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Rheumatologist
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have read the British Society for Rheumatology (BSR) response to this appraisal and agree wholeheartedly with it. As someone who regularly sees and treats patients with giant cell arteritis (GCA) I can attest to the fact that there are refractory patients who relapse and who require an unacceptably high dose of corticosteroid (CS) with its attendant consequences of osteoporosis, diabetes, skin fragility etc. I am confident when the factors pointed out in the BSR response are taken into account the balance of cost effectiveness will swing toward using Tocilizumab in refractory and CS resistant GCA

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I wish to express my strong support for the initiative proposing the use of Tocilizumab for treating giant cell arteritis [ID1051]. As a Consultant Rheumatologist who sees an appreciable number of patients with this condition I like many of colleagues recognise the urgent need for medications other than chronic steroids for the induction and maintenance of disease activity remission in this very serious illness. We are familiar with the central role for steroids in giant cell arteritis and of the pivotal importance of starting this medication as a matter of urgency particularly in individuals in who ischaemic symptoms are threatening vision. Despite the clear benefits for steroids there is an appreciable number of patients who relapse or are refractory to high dose oral steroids which in some cases requires even greater steroid burden through IV administration. There remains an unmet need in the management of this condition for alternative treatments which not only are proven to modulate chronic inflammation but will overall offer a much safer therapeutic option for the treatment of giant cell arteritis. The side effect profile of chronic steroid requirement is without doubt with potentially devastation consequences for the patient, the patient's family and society through increased stress on already stretched resources through management for avoidable steroid-induced comorbidities. I fully support the use of Tocilizumab as a therapeutic strategy for the management of giant cell arteritis.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Rheumatologist
Organisation	[redacted]
Location	England
Conflict	[redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Given the serious complications associated with GCA, it is imperative to control inflammation. The current management with high-dose Glucocorticoids leaves the following significant unmet needs: 1. Effective treatment of refractory patients who are not responsive to glucocorticoids (10-17% of the cohort) 2. Effective treatment of partial-responders who respond only to long-term, high-dose glucocorticoids 3. Effective management of patients accruing aortic, or other large vessel, damage, despite apparent response to glucocorticoids/conventional immunosuppressants. 4. Cost-effective management of relapsing patients who require repeated review and, often long-term, high-dose glucocorticoids 5. Management of patient in whom Glucocorticoids are contra-indicated 6. Reduction of the human and economic cost of the high burden of glucocorticoid-related morbidity, particularly in the older demographic affected by GCA. The GiACTA study provides substantial new evidence for the efficacy of Tocilizumab in GCA and this new data should be considered. We propose that a panel of clinicians with expertise in GCA work with NICE to determine eligibility and response criteria to enable a trial of Tocilizumab to be available for the following patient categories, each requiring careful definition. 1. Refractory patients 2. Partial-responders 3. Patients with progressive large vessel damage 4. Relapsing patients 5. Patient with contra-indication for use of glucocorticoids Perhaps a six month trial of Tocilizumab could be funded initially, to establish patient response, with review at an MDT after a further six months. Research questions should be indentified, which will enable the GCA investigators to determine how the cost-effectiveness of the treatment with Tocilizumab may be optimised.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Professor of Rheumatology
Organisation	[redacted]
Location	England
Conflict	[redacted]
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I [redacted] would like to fully endorse [the BSR] literature review, comments and proposals on behalf of the UK GCA Consortium and MRC TARGET (Treatment According to Response in Giant Cell Arteritis) Partnership [redacted]. As a practicing clinician I cannot emphasise enough the major impact that high-dose glucocorticoids have on the quality of life of patients with GCA. I do not feel that the serious nature of some of these adverse events has been fully taken into account in the modelling presented in the consultation document. Some adverse events are severe enough to require acute hospitalisation, such as psychosis, serious infections, perforations, gastrointestinal bleeds, fractures, avascular necrosis, decompensated heart failure and myocardial infarctions. Many older patients with fractures and avascular necrosis are unable to return to independent living and require long-term residential care. Serious morbidity and reduced independence also arises from steroid myopathy/ sarcopenia and skin fragility and poor wound healing or from complications such as a ruptured Achilles tendon. These complications are less well studied and so have not been captured in the economic models, yet have a profound impact on GCA patients and their families. Glucocorticoid toxicity has primarily been studied in the context of RA, yet GCA patients are older and receive much higher doses. Older people are reported to be more vulnerable to the adverse effects of glucocorticoids, which occur in up to 86% of patients, with 70% of GCA patients experiencing two or more events. This fits with my clinical experience where I see the most severe glucocorticoid toxicity in patients with GCA. The elderly population have an increased frequency of co-morbidities making treatment decisions difficult for clinicians with a tendency for undertreating the underlying vasculitis for those patients with the most severe adverse events. Uncontrolled inflammation and accrued vascular damage causes serious morbidity, including a 17-fold increased risk of thoracic aortic aneurysm, dissection and rupture in addition to the vascular stenoses observed in patients with the most severe large vessel GCA. A lack of a proven treatment alternatives means that high-dose glucocorticoids remain standard therapy. This is in marked contrast with other inflammatory disorders/ vasculitides affecting younger patients where introduction of early immunosuppressive therapy has been proven to lead to improved patient outcomes. The MRC acknowledged that there was a compelling need for the identification for new diagnostics and therapeutics for GCA and provided funding to establish the TARGET partnership. Our primary aim is reduce glucocorticoid toxicity in GCA patients through the identification of clinical and molecular strata that could be used for treatment stratification, novel diagnostic and prognostic biomarkers, novel treatment targets and innovative approaches to clinical trial design.

	The TARGET Partnership includes representation from relevant UK academic and clinical groups including Arthritis Research UK Clinical Studies Group for Autoimmune Rheumatic Disorders ([redacted], [redacted], [redacted]), RCOphth Science ([redacted]), British Ophthalmology Surveillance Unit ([redacted], [redacted], [redacted]), NHS England ([redacted]), British Association for the Study of Headache ([redacted]), British Vascular Society ([redacted]), British Society for Rheumatology ([redacted]), UKIVAS ([redacted], [redacted], [redacted]) and OMERACT Working Group on Glucocorticoid-related Adverse Effects ([redacted], [redacted]). Patient groups have been integral to developing our research agenda (VasculitisUK, UKiVAS, Fight for Sight) Through this MRC funding we will be combining the data from four large GCA/ vasculitis cohort studies have been established in the UK, two with associated biobanks. The UKGCA consortium (>1800 participants from 24 centres) has recently obtained ethical approval for research access to e-health records (including linkage) where we plan to explore the prevalence of glucocorticoid toxicities and other pharmacological therapies, in addition to performing epidemiological analyses. We have established a programme of work where we plan to obtain more accurate estimates of the incidence of glucocorticoid-related adverse effects in GCA to inform the parameters of decision analysis models and Health Economic analyses. This work also includes the study of risk factors for different types of toxicities and the development of risk prediction tools to identify patients with increased risk of toxicity. We have already obtained data from CPRD (linked to HES and the mortality registry) and UKBiobank and are in the process of developing algorithms to model glucocorticoid dose and duration and to develop new methodology to study less frequently investigated toxicities, such as serious infections, adrenal insufficiency, chronic skin ulceration and sarcopenia. We have also been in discussion with the Pharmaceutical Industry with a view to obtaining data on patients receiving glucocorticoids during clinical trials. We will be submitting funding proposals in the form of Fellowships and project grants to model the impact of gender, age, co-morbidity, underlying diagnosis and concomitant medications in addition to glucocorticoid dose and duration using both clinical trial datasets and routinely-collected clinical data. This programme of work has only recently started and so unfortunately we are not currently in a position to provide any unpublished data to the NICE review board. However, we would be more than happy to work with NICE in the future to ensure that future modelling includes more accurate toxicity or epidemiological data from individuals with GCA. The UKGCA Consortium, with existing ethical approval for electronic health record linkage and tissue and DNA Biobanks is also ideally suited for performing post-marketing surveillance of Tocilizumab in routine clinical practice and is already recruiting from over 30 centres in the UK. Additional funding would be required for the maintenance and management of this repository and for linkage and analytical time, but this would offer significant cost savings over the establishment of a new database for this purpose. We fully endorse the BSR position that GCA subgroups, such as patients with frequent disease relapses or who are refractory to glucocorticoids and those with contra-indications to long-term glucocorticoid therapy, have not been separately considered in this NICE consultation. Treatment with Tocilizumab of these subgroups is efficacious, safe

	and cost effective since the costs averted of glucocorticoid toxicity, ischaemic complications, and vascular damage, are high to the patients, their family and society. We strongly urge NICE to support access to short-term use of Tocilizumab as recommended by the BSR for those patients with the most severe disease or glucocorticoid adverse events.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Professor of Clinical Autoimmunity
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	1. Section 3.5: I disagree with the clinical experts that the duration of steroids for uncomplicated GCA is 18-24 months. This is historic practice and there is a trend to lower doses and shorter courses as used in the GIACTA protocol.
Section 2 (The technology)	2. The need for newer therapies is more acute for refractory disease and those in whom steroids are contra-indicated. A wide variety of drugs are used in this setting, including immunosuppressives (methotrexate, cyclophosphamide, mycophenolate etc) and biologics, (anti-TNF, anti-IL6r, rituximab). Such patients represent a major part of the GCA referrals to tertiary vasculitis clinics and will benefit most from tocilizumab, and there will be a different cost-effectiveness result. I recommend such patients are treated as specific subgroups, are excluded from a blanket 'do not fund tocilizumab', recommendation. Clearly, further evidence in terms of both benefits and costs for these subgroups are needed.
Section 3 (The manufacturer's submission)	3. UKIVAS. A vasculitis physician network in the UK and Ireland has not been consulted and would be the most appropriate source for a consensus up to date view from UK experts.

Appendix 1: Revision of the cost-effectiveness model

A1.1 A corrected cost-effectiveness model has been shared with NICE

Two errors have been identified in this model and amended to give a deterministic ICER of £25,929 for 12 months tocilizumab treatment in relapse/refractory GCA patients (**Error! Reference source not found.**). Firstly, an average UK population weight was used to calculate the dosages of concomitant medications, whereas the weight of the GiACTA relapsing/refractory population is more appropriate. This has been amended in the 'Cost inputs' tab, cell H118. Secondly, the annual concomitant medication costs applied to the placebo arm was erroneously divided into weekly costs twice. This was corrected in the 'CS (52Wk) arm' tab, cells BK12 to BK1681.

Table 1: 12 months tocilizumab treatment in relapsed/refractory GCA patients – amended model errors (with PAS)

Treatment	QALYs	Incremental QALYs	Costs	Incremental costs	Deterministic ICER
Prednisone only	7.17	0.15	[redacted]	£4,003	£25,929
Tocilizumab with prednisone	7.32		[redacted]		

A1.2 The steroid taper has been amended to reflect NHS clinical practice

Roche recognise the Committee's concerns regarding the relevance of the 52-week steroid tapering regimen in the control arm of the GiACTA trial, as discussed in Comment 4 above. Therefore, a longer tapering regimen has been incorporated into the amended model, which matches the British Society for Rheumatology GCA treatment Guidelines. This 'slowest' BSR tapering regimen is detailed in Comment 4.3. Amending the modelled steroid-taper to reflect NHS practice in this way gives a deterministic ICER of £24,008/QALY (**Error! Reference source not found.**).

Table 2: 12 months tocilizumab treatment in relapsed/refractory GCA patients – steroid tapering regimen adjusted to better reflect NHS clinical practice, using the 'slowest' BSR recommended tapering regimen (with PAS)

Treatment	QALYs	Incremental QALYs	Costs	Incremental costs	Deterministic ICER
Prednisone only	7.17	0.15	[redacted]	£3,707	£24,008
Tocilizumab with prednisone	7.32		[redacted]		

A1.3 NHS management costs for GCA are here fully costed

In the original submission, to allow for a conservative estimate of costs associated with GCA flares/relapses, the presentation rates to Accident and Emergency on recurrence of symptoms was combined with visits to 'other' clinicians, costed at £164 per visit (Curtis et al 2017). However, to aid the Committee's decision making and give more granularity to the benefits of tocilizumab and costs of current GCA care to the NHS, these are separated here to fully capture the presentation rates reported in the market research (Curtis et al 2017).

The 7% 'other' appointments originally modelled to manage relapse/flare is here more precisely costed as 2% 'other' clinicians and 5% presentation to Accident and Emergency (Curtis et al 2017). The PSSRU average cost of an Accident and Emergency visit is £1,006, giving a more accurate calculation of the management costs of a

GCA flare to the NHS currently (Curtis et al 2017). The PSSRU reports Accident and Emergency costs for patients over 75 years of age as £1,081, however the lower value is used here to be conservative (Curtis et al 2017).

The management costs associated with the non-flare health states only have 1% presentation at recurrence for the 'other' and Accident and Emergency visits, so these have not been separated here (**Error! Reference source not found.**).

Including costs for Accident and Emergency presentation at relapse increases the deterministic ICER to £23,244/QALY.

Table 3: 12 months tocilizumab treatment in relapsed/refractory GCA patients– with management costs better specified to incorporate Accident and Emergency visits currently occurring in the NHS for GCA patients (with PAS)

Treatment	QALYs	Incremental QALYs	Costs	Incremental costs	Deterministic ICER
Prednisone only	7.17	0.15	[redacted]	£3,590	£23,244
Tocilizumab with prednisone	7.32		[redacted]		

A1.4 GC-related AE costs have been updated to reflect 2017 health care resource utilisation

In the original model, the costs for osteoporosis management, diabetes care, fractures and infections were considered conservatively. However, to allow NICE to consider the full, current costs of GCA care to the NHS, these costs have been inflated to 2017 health care utilisation costs using the PSSRU (Curtis et al 2017).

Osteoporosis costs: previously only 2 clinician appointments were costed, however Guidelines recommend DEXA scans and prophylaxis medication be prescribed also. Dunstan et al 2013 reported 67.6% of GCA patients receive anti-osteoporosis treatments, demonstrating this guidance is applicable to GCA patients (Kanis et al 2007, NICE Clinical Guideline 146, NICE TA160).

Diabetes costs: previously the diabetes care costs were incorporated directly from the 2005 publication, here these same costs are inflated to 2017 health care resource use.

Fracture costs: previously the fracture costs were sourced from published literature for post-menopausal women over 50 years of age (Luqmani 2016). However, a more targeted literature search identified fracture costs resulting from steroid treatment, specifically for patients 65 - 74 years old (Kanis et al 2007) which were then inflated to 2017 costs using PSSRU inflation rate for health care resources (Curtis et al 2017).

Infection costs: previously the costs for infections were derived from standardised NHS costs from the National Schedule of Reference Costs. Here a targeted literature search supports higher costs for some GC-related infections, specifically tuberculosis, sepsis and pneumonia (Sarnes 2011).

The above costs have been jointly incorporated to give a deterministic ICER of £19,348/QALY (**Error! Reference source not found.**).

Table 4: 12 months tocilizumab treatment in relapsed/refractory GCA patients – incorporating costs published in relation to GC-related AEs (with PAS)

Treatment	QALYs	Incremental QALYs	Costs	Incremental costs	Deterministic ICER
Prednisone only	7.17	0.15	[redacted]	£3,002	£19,348
Tocilizumab with prednisone	7.32		[redacted]		

A1.5 GCA relapse/flare rate is amended to better reflect GiACTA data

The cost-effectiveness model amended here uses the flare/relapse rates incorporated by the ERG, based on Labarca 2016 – this represents the Committee's preferred assumptions. To fully account for the relapsed/refractory population we applied a 10% adjustment to the relapse/flare rate incorporated by the ERG. This is to account for the incremental difference observed between the ITT and relapsed/refractory patients in the prednisone arm of the GiACTA trial. Roche believes this is a better estimate of the rate of flares in control arm of the relapsed/refractory population. The deterministic ICER following this 10% flare rate adjustment is £18,801 (**Error! Reference source not found.**).

Table 5: 12 months tocilizumab treatment in relapsed/refractory GCA patients – amended flare rate for relapsed/refractory patients receiving placebo, based on Labarca 2016 and GiACTA data analysis (with PAS)

Treatment	QALYs	Incremental QALYs	Costs	Incremental costs	Deterministic ICER
Prednisone only	7.16	0.16	[redacted]	£2,959	£18,801
Tocilizumab with prednisone	7.31		[redacted]		

A1.6 Not all cost and utility evidence can be incorporated into the ICER calculation

The updates to the cost-effectiveness modelling detailed above are based on high level evidence and require few assumptions to incorporate into the model. There is further evidence of the benefits of tocilizumab in GCA patients, which would improve the accuracy of the ICER estimate for NICEs consideration. However, these would require more assumptions in order to allow their incorporation into the model. This further evidence is described below, to allow NICE to fully consider the clinical and cost-effectiveness to fully inform guidance development.

A1.6.1 Costing the benefits of tocilizumab in GCA patients

During the Appraisal Committee Meeting, the Committee raised questions regarding GC-related AEs and the costs of treating these, which Roche believes to be conservative. A more comprehensive costing analysis cannot be incorporated herein since few published AE event rates are linked to cumulative steroid burden. This is why only the costs for AEs reported in the CPRD analysis of GCA patients were included in the cost-effectiveness model, specifically fracture, osteoporosis, infection and diabetes (Wilson 2017).

Steroid treatment is however, associated with numerous AEs, as described in Comment 5.4. All of these AEs will have an associated risk for GCA patients and a cost to the NHS, but since the model is structured to

account for cumulative steroid burden and the GiACTA trial lasted only 12 months, not all of these AEs are clearly evidence to accurately calculate the impact on the ICER. Yet, it is plausible that there are more costs associated with steroid AEs than are modelled here, and that tocilizumab treatment would avoid a proportion of these additional costs by limiting steroid exposure.

This underestimate of costs associated with steroid AEs, is similarly plausible for GCA complications, for example surgery costs for aortic aneurism treatment. The costs for such interventions have not been included here, as it is unclear what the incidence of these interventions are, and how this is linked to the benefits of improved GCA disease control associated with tocilizumab treatment. Furthermore, hospitalisation rates for GCA patients are significantly higher than for matched controls (Wilson 2017), however the uncertainties around the costs of these hospitalisations limit the modelling of the potential benefits of tocilizumab in controlling flares/relapses in GCA.

Clinical opinion also stated that during a flare, a patient could receive blood tests, chest x-rays, and urine tests to look for signs of infection. However, it is unclear whether all clinicians and all Trusts perform these tests routinely when a patient present's with returned signs and symptoms. So again, this represented potential additional costs of flare avoidance that are not fully captured for tocilizumab treatment of GCA patients.

A1.6.2 GC-related AE disutility

In the current model, a GCA patients' quality of life is reduced by the occurrence of disease flares/relapses and also by steroid-related AEs. The disutility value incorporated for GCA patients experiencing a steroid-related AE was taken from published literature (Niederkohr and Levin, 2005). However, this published disutility only included the following steroid-related AEs, while we know many more AEs can result from steroid treatment:

- Hyperglycemia/diabetes,
- Vertebral fracture,
- Hip/femoral neck fracture,
- Avascular necrosis of femoral head,
- Infection (requiring hospitalization),
- Peptic ulcer disease,
- Hypertension (requiring treatment),
- Steroid myopathy,
- Psychiatric disturbance.

This is a comprehensive list of steroid-related disutilities, but it is not an exhaustive list, therefore the benefits of tocilizumab in limiting steroid exposure is plausibly underestimated. For example, depression and weight gain are two well characterised steroid-related AEs which are likely to impact a GCA patient's quality of life. However, since these have not been incorporated into the cost-effectiveness model, the calculated ICER is likely to be an underestimate. These additional disutilities have not been modelled here, since too many assumptions would need to be made regarding the incorporation of the benefits reported in the literature into the current model.

A1.6.3 Adopting a conservative approach to high cost patients

The PSSRU reports separate costs for "high-cost patients discharged from Acute Medical Unit (top 25% of most costly patients - costs have been updated using the HCHS inflator)" (Curtis et al 2017). Since GCA patients are typically elderly and have serious co-morbidities and complications, it seems plausible that some GCA patients will meet these criteria. However, it is unclear how many, and how to identify these patients. If these PSSRU costs for "high cost" patients were applied to all GCA patients, the deterministic ICER for 12 months tocilizumab treatment in relapsed/refractory patients would be £4,065/QALY.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's response to ACD comments
Tocilizumab for treating giant cell arteritis

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1 Summary

Following the first appraisal meeting of tocilizumab for treating giant cell arteritis (GCA), Roche (the company) made a request to submit revised economic analysis and additional evidence to support the clinical and cost-effectiveness of tocilizumab. The company's response covered eight issues:

1. GCA pathophysiology: the burden on patients and the NHS
2. Patient sub-populations: identifying the greatest unmet need
3. Treatment goal in GCA: reduction in cumulative steroid burden
4. Current standard of care: steroid tapering regimens
5. Steroid-related adverse events: the seriousness is understated
6. Clinical effectiveness of tocilizumab: impact on steroid-related toxicities
7. Duration of tocilizumab treatment: 12 months of tocilizumab is efficacious and cost-effective
8. Revision of the cost-effectiveness model

The ERG was requested by NICE to provide commentary and validity checks on the revised analyses and model submitted in response to the ACD.

The revised economic model proposed further revisions to the ERG's alternative base-case analysis and preferred assumptions for 12 months tocilizumab treatment for relapsed/refractory GCA patients only.

Table 1 summarises the revised company base-case assumptions and the ERG's critique.

Table 1: Summary of ERG critique of company revised base case.

Issues	Revised company base case assumption	ERG critique
(1) Revised base-case based on 12 months tocilizumab treatment for relapsed/refractory patients only	• Based on the committee's preferred assumptions in the ERG's model for 12 months tocilizumab treatment for relapsed/refractory GCA patients only.	The original company submission assumed that treatment with tocilizumab stops after 2 years. The committee previously concluded that the average treatment duration with tocilizumab was likely to be at least 2 years, and could be longer (paragraph 3.9, ACD). The company response to ACD requests that the committee reconsider this position, stating that both the company and clinical experts consider that 12 months treatment would provide clinically relevant efficacy and be a responsible use of NHS resources. The ERG notes that no new evidence was used to inform the clinical efficacy assumptions applied within the revised model.
(2) Corrections to the cost-effectiveness model	• Average UK population weights were previously used to calculate the	The ERG does not consider that this is an error as the original submission clearly

	dosages of concomitant medication. The company response proposed that the average weight of GiACTA relapsed/refractory population should be used.	stated the source and assumptions applied. However, the ERG accepts that using weight estimates specific to the relapsed/refractory population appears appropriate. The ERG also notes that the company only revised the weight estimates and not the body surface areas (BSA) estimates. The ERG considers that it would be consistent to alter both weight and BSA estimates.
	• Annual concomitant medication costs applied to the prednisone alone arm was incorrectly divided into weekly costs twice.	The ERG notes that this error was present in the original company submission and was not identified by the company or ERG during the initial assessment. The ERG agrees that this is a programming error and accepts the company revisions. However, the ERG also notes that a further error remained in the company's revised analysis, as the revisions did not appropriately account for mortality. The ERG proposed a further correction to account for this.
(3) Amendments to the steroid taper regimen in the control arm of GiACTA to reflect NHS clinical practice.	• The revised model includes a longer tapering regimen which matches the 'slowest' tapering regimen in BSR guidelines.	The committee was concerned that the 52 week (12 month) tapering strategy reflected the minimum taper regimen recommended by the BSR (Section 3.5 ACD). The committee considered that this might mean that the number of flares in the comparator arm may be higher, and the time to first flare shorter, than in clinical practice in England. The ERG notes that the company amendments only adjust the cost of the comparator steroid-taper regimen and no adjustment is proposed to address the committee's uncertainties regarding the possible impact on clinical efficacy. The ERG does not consider that the revisions address the committee concerns and do not agree with the amendment proposed by the company.
(4) Amendments to the NHS management costs for flare/relapse	• Additional granularity is applied to the costs of 'other' appointments. The 7% of patients receiving 'other' appointments were previously costed at £164 per visit. The company proposed more precise unit cost estimates for these appointments, noting that 5% of patients presented to Accident and Emergency and 2% to 'other' clinicians.	The ERG accepts that further precision may help to provide additional granularity in the cost estimates. However, the ERG does not accept the revised unit cost estimate for Accident and Emergency visits (£1006, Curtis et al, 2017) proposed by the company. The ERG checked the reference provided and notes that the estimate of £1,006 appears to refer to a combined estimate of the annual cost of Accident and Emergency and outpatient care. The ERG proposes an alternative estimate for an Accident and Emergency visit of £146.86, based on NHS reference costs.
(4) Amendments to GC-related AE costs to reflect 2017 health care resource utilisation	• *Osteoporosis costs* were revised to include additional costs for an annual DEXA scan (£62) and prophylaxis medication (annual costs £296.40).	The ERG notes that the costs of osteoporosis are assumed to apply for the remainder of a patient's lifetime (or the model horizon). The ERG does not believe that DEXA scans would be

		undertaken repeatedly on an annual basis and notes that the annual costs proposed for prophylaxis medication were markedly higher than the average generic costs of oral therapies applied in NICE TA 464 (£296.40 vs £13.32). The ERG proposed additional adjustments assuming the costs of a one-time DEXA scan and using the annual average generic cost estimate for oral therapies of £13.32 for consistency with TA 464.
	• *Diabetes costs* were inflated from 2005 to 2017 estimates.	The ERG considered this to be an appropriate adjustment.
	• *Fracture costs* were revised based on a targeted literature review and sourced from a reference specifically for patients 65-74 years old (Kanis et al 2007).	No details were provided on the targeted literature review and the reference provided was from 2007. The ERG proposed alternative estimates consistent with those used in TA 464.
	• *Infection costs* were revised based on a targeted literature review. The company proposed higher estimates for some GC-related infections (Sarnes, 2011).	No details were provided on the targeted literature review or the specific basis for the alternative estimates. The ERG notes that the reference provided (Sarnes, 2011) is a US study and the generalisability of the findings to the NHS is unclear. In the absence of further evidence on the generalisability of this source, the ERG did not consider this to be an appropriate adjustment.
(5) GCA relapse/flare rate amended to better reflect GiACTA data	• The revised model included an amendment to the flare/relapse rate estimates proposed by the ERG. A 10% adjustment was applied to the relapse/flare rate estimates used by the ERG.	No errors or uncertainties were identified regarding the ERG's previous approach. The ERG notes that the company estimates do not incorporate any new evidence and hence are unclear why any additional adjustment is necessary or appropriate.

The company presented revised ICER estimates relating to each of the issues summarised in Table 1. The company also reported a revised (deterministic) base-case ICER combining all of their proposed amendments. The company's estimate of the revised base-case ICER of 12 months tocilizumab treatment for relapsed/refractory GCA patients was £18,801 per QALY.

The ERG notes that the company submission (p3 and p20) refers to a revised base-case ICER of £18,898 per QALY. The ERG considers that this is a reporting error and the correct estimate should be £18,801 per QALY (as reported in Table 11 of the company report and the accompanying Excel model). The ERG also notes minor discrepancies in the costs reported in Table 11 of the company report and the Excel model, although the same ICER of £18,801 is reported in both.

The ERG's alternative estimates of the revised base-case ICER of 12 months tocilizumab treatment for relapsed/refractory GCA patients were £24,977 per QALY (deterministic) and £24,032 per QALY (probabilistic). These estimates combined all of the amendments considered appropriate by the ERG.

The ERG previously concluded that the 1-year treatment period results provided the most internally valid estimates consistent with the treatment duration period assessed in the GiACTA trial. However, uncertainty may remain concerning the extent to which the duration will be rigorously adhered to in clinical practice. The ERG also provided estimates of the revised base-case ICER for a 2-year treatment duration period for relapsed/refractory GCA patients. The ICER estimates were £55,924 per QALY (deterministic estimate) and £55,076 per QALY (probabilistic estimate). The differences reported between the 1 and 2-year treatment duration periods clearly highlight the importance on ensuring that any potential guidance concerning shorter treatment duration periods are fully adhered to in clinical practice.

2 Critique of the company response to the ACD – clinical effectiveness

2.1 GCA pathophysiology: the burden on patients and the NHS

The company considers that the severity of GCA physiology has not been represented in its full extent in the ACD and requests that this is addressed by the committee in its reconsideration of the evidence. The company reported a new population-based cohort study by Mohammad et al on co-morbidities in GCA. However, the company also states that the results of this cohort study are similar to those previously reported by Petri et al., which was originally included in the company submission and the ERG report. Therefore, the ERG believes that there was no new significant evidence provided in the ACD response on the severity of GCA physiology.

2.2 Patient sub-populations: identifying the greatest unmet need

The company agrees with the committee that tocilizumab would be most valuable for patients with relapsing or refractory GCA and therefore the company's amended cost-effectiveness model is targeted to this subgroup only. The company also considers that there is also clinical plausibility for a subset of patients with newly-diagnosed GCA for whom tocilizumab would be valuable, for e.g. patients with pre-existing cardiovascular risk, osteoporosis, obesity and diabetes. However, robust evidence for these subgroups is lacking and no new evidence was provided in the ACD response.

2.3 Treatment goal in GCA: reduction in cumulative steroid burden

The company agrees that the reduction in cumulative steroid burden is a valid and clinically significant treatment goal. However, the company considers that this has not been reflected in subsequent parts of the ACD and requests that this treatment goal is addressed in the committee's considerations. The ERG believes that this is an issue with the wording of the ACD and notes that no new evidence is provided in the ACD response.

2.4 Current standard of care: steroid tapering regimens

The committee was concerned that the 52 week (12 month) tapering strategy reflected the minimum taper regimen recommended by BSR guidelines (Section 3.5 ACD). The committee considered that this might mean that the number of flares in the comparator arm may be higher, and the time to first flare shorter, than in clinical practice in England.

In their response, the company accepts that tapering steroids over 52 weeks may not reflect current real world clinical practice in the NHS. The company proposed a revision to the prednisone-only arm of the cost-effectiveness model to incorporate the slowest possible tapering regimen recommended by the BSR guidelines, which now takes up to 2 years. The ERG notes that the company revisions only adjust the cost of the comparator steroid-taper regimen and no adjustment is proposed to address the committee's uncertainties regarding the possible impact on the number of flares and time to first flare.

The ERG does not consider it appropriate to alter the costs of the comparator regimen without any additional adjustment to the clinical efficacy data.

The company provided new evidence on the baseline remission status of patients in GiACTA. The ERG previously noted there might be a potential bias in the primary end point in favour of tocilizumab. This was due to 49% of patients in the comparator arm not achieving remission at baseline but having to start the 52-week tapering regimen. Roche have provided a new exploratory analysis, stating that there is no difference in primary endpoint when analysing by remission status at baseline. The exploratory analysis shows that of the patients who were not in remission at baseline, 16% achieved sustained remission at week 52 in the comparator arm and 52.3% in the intervention arm. Whereas, of the patients who were in the remission at baseline, 19.2% achieved sustained remission at 52 weeks in the comparator arm and 60% in the intervention arm. Roche did not provide any statistical tests to support the conclusion that there was no difference in primary endpoint. However, numerically the evidence does not appear to negate the ERG's concerns of a potential bias as fewer patients in the comparator arm who were not in remission at baseline achieved sustained remission at week 52 compared to patients who were in remission at baseline.

2.5 Steroid-related adverse events: the seriousness is understated

The company considers that the ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients. The ERG believes that this is an issue with the wording of the ACD and that the seriousness of steroid-related AEs has been clearly described in the ERG report. Furthermore, the company presents no new substantial evidence provided in the ACD response on the seriousness of steroid-related adverse events. Some of the sources stated in the response are studies that have already been used in the company submission and the model (for e.g. Table 4 Wilson et al. 2017). Evidence from new sources appears largely to support what was already reported in the company submission.

2.6 Clinical effectiveness of tocilizumab: impact on steroid-related toxicities

The company considers that there is robust clinical evidence for the impact of tocilizumab on cumulative steroid burden and steroid-related AEs. The company requests that this be reflected in the committee's reconsideration of the evidence.

In the GiACTA study there was a similar rate of steroid-related AEs in both arms; 49% in the placebo arm and 50% in the tocilizumab arm. Roche have provided new post-hoc analyses on the rates of steroid-related toxicity. The results show [redacted]. However, the company does not provide any statistical tests to support this difference in steroid-related toxicity between arms. Furthermore, these data were analysed

retrospectively and were not based on standard or pre-specified criteria. Although, it is logical to assume that there would be lower steroid related AEs in the tocilizumab arm compared to the placebo arm due to the lower median cumulative steroid dose in the tocilizumab arm, the GiACTA trial showed no differences based on standard and pre-specified criteria. Therefore, the ERG does not consider these new analyses provide robust additional evidence. Despite these uncertainties, the ERG would like to highlight that the model incorporates external data on the relationship between cumulative steroid dose and steroid related AEs and hence considers that the potential impact has been quantified with the cost-effectiveness results.

2.7 Duration of Tocilizumab treatment: 12 months of tocilizumab is efficacious and cost-effective

The committee previously concluded that the average treatment duration with tocilizumab was likely to be at least 2 years, and could be longer (paragraph 3.9 ACD). The company considers that 12 months of tocilizumab treatment would provide clinically relevant efficacy and requests that the committee reconsider their position. The company provided new evidence from a literature review of published case reports of the use of tocilizumab in GCA, which were not provided in the original company submission.

In these case reports, 109 patients with GCA had been treated with tocilizumab for time periods ranging from 1 to 53 months, with the majority receiving tocilizumab for much less than one year. The company provides details about one of the larger case reports by Regent et al., reporting that 34 patients had a mean treatment time with tocilizumab of 6.4±4.5 months with a median follow up of 13 months. However, the company does not provide details or follow up times for the other case reports or the treatment intent regarding the planned duration of tocilizumab treatment. Follow up completeness is necessary for reliable outcome assessment and credibility of evidence. The ERG is also aware that these case reports may have been used to verify the duration of tocilizumab in the GiACTA trial. Considering that case reports are a lower level of evidence with less validity than randomised trials and the lack of follow up details provided by the company, the ERG believes that there is not sufficient information provided to fully address the uncertainties noted by the committee.

3 Critique of company's response to the ACD – cost effectiveness

3.1 Overview

The company response to the ACD included a revised cost-effectiveness model based on the ERG's alternative base-case. The revised model was based on the ERG's alternative base-case estimates previously reported for 12 months of tocilizumab therapy for relapsed/refractory GCA patients.

Table 2 and Table 3 summarise the alternative base-case ICERs (deterministic and probabilistic) previously reported by the ERG for a 1-year treatment duration of tocilizumab for the relapsed/refractory population.

Table 2: ERG alternative base-case *deterministic* results (1-year treatment duration) – Relapsed/refractory subgroup

	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	8.72	[redacted]	10.78	7.17	-1.42	£4,713	0.00	0.15	£30,528
Tocilizumab with prednisone	7.30	[redacted]	10.78	7.32					

Table 3: ERG alternative base-case *probabilistic* results (1-year treatment duration) – Relapsed/refractory subgroup

	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	8.57	[redacted]	10.54	6.99	-1.40	£4,638	0.00	0.15	£30,158
Tocilizumab with prednisone	7.16	[redacted]	10.54	7.14					

In their response, the company identified two programming errors which were amended. The company also proposed a series of additional amendments to address issues raised in the committee meeting. The combined corrections and amendments resulted in a revised (deterministic) ICER of £18,801 per QALY, including the confidential Patient Access Scheme (PAS).

Although the company state that the model was revised to incorporate new evidence, the ERG notes that the new evidence largely comprised revised and/or more granular cost estimates and that no additional clinical evidence reported in the clinical effectiveness sections were included in the revised model. The ERG also considers that several of the proposed amendments did not appear to directly address issues raised in the committee meeting.

The ERG successfully replicated the company's revised results. The ERG also undertook a series of additional validity checks of the revised model as well as providing a critique of the proposed amendments and revisions. Alternative ICER estimates were also provided.

3.2 Corrections for programming errors

The company noted that two programing errors were identified in the model and the proposed corrections resulted in a deterministic ICER of £25,929 for 12 months tocilizumab treatment in relapse/refractory GCA patients.

The first error related to the use of the average UK population weight which was previously used to calculate the dosages of concomitant medication. The company response proposed that using the average weight of GiACTA relapse/refractory population would be more appropriate. The ERG does not consider that this is an error as the original submission clearly stated the source and assumptions applied. However, the ERG accepts that using weight estimates specific to the relapse/refractory population appears appropriate. The ERG also notes that the company only revised the weight estimates but not the body surface area (BSA) estimates. The ERG considers that it would be consistent to alter both weight and BSA estimates. Adjustments for both weight and BSA estimates were included in the ERG's proposed revisions.

The second error identified was that the annual concomitant medication costs applied to the prednisone alone arm was incorrectly divided into weekly costs twice. The ERG notes that this programming error was present in the original company submission and was not identified by the company or ERG during the initial assessment. The ERG agrees that this is a programming error and accepts the company revisions. However, the ERG also notes that a further error remained in the company's revised analysis, as the proposed revisions do not appear to account for mortality. The ERG incorporated a further correction to account for mortality.

Table 4 summarises the revised ICER based on ERG's preferred corrections addressing the errors identified by the company. These corrections result in a deterministic ICER of £26,938 per QALY.

Table 4: ERG alternative (deterministic) ICER estimates incorporating proposed corrections

	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	8.72	[redacted]	10.78	7.17	-1.42	£4,159	0.00	0.15	£26,938
Tocilizumab with prednisone	7.30	[redacted]	10.78	7.32					

3.3 Amendment to the steroid taper regimen in the control arm of GiACTA to reflect NHS clinical practice

The ERG notes that the company amendments only adjusted the cost of the comparator steroid-taper regimen and no adjustment was proposed to address the committee's uncertainties regarding the possible impact on clinical efficacy.

The ERG does not consider that the revisions address the committee concerns and do not agree with the amendment proposed by the company.

3.4 Alternative NHS management costs for relapse/flare

The company proposed an amendment to the costs of 'other' appointments, applied to 7% of patients experiencing a relapse/flare, to give a more accurate estimate of the management of relapse/flare costs to the NHS. The company noted that their original submission provided a conservative estimate of the costs of relapse/flare by applying a single unit cost estimate of £164 per visit (Curtis et al, 2017). The company proposed more precise unit cost estimates for these appointments, noting that the estimate of 7% actually comprised 5% of patients presenting to Accident and Emergency and 2% to 'other' clinicians. The company proposed an alternative unit cost estimate for Accident and Emergency visits of £1,006 (Curtis et al 2017).

The ERG accepts that further precision may help to provide additional granularity in the cost estimates. However, the ERG does not accept the revised unit cost estimate for Accident and Emergency visits (£1006, Curtis et al, 2017) proposed by the company. The ERG checked the reference provided and notes that the estimate of £1,006 appears to refer to a combined estimate of the annual cost of Accident and Emergency and outpatient care. The ERG proposed an alternative estimate for an Accident and Emergency visit of £146.86, based on NHS reference costs.

Table 5 summarises the revised (deterministic) ICER results based on the alternative unit cost estimate from NHS reference costs for an Accident and Emergency visit. These results also include the corrections proposed by the ERG to address the errors identified by the company and discussed in the previous section.

Table 5 : ERG alternative (deterministic) ICER estimates incorporating revised unit costs for Accident and Emergency visits and previous corrections

	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	8.72	[redacted]	10.78	7.17	-1.42	£4,161	0.00	0.15	£26,951
Tocilizumab with prednisone	7.30	[redacted]	10.78	7.32					

3.5 GC-related AE costs updated to reflect 2017 health care resource utilisation

The company proposed a series of amendments to more appropriately reflect current costs to the NHS.

- *Osteoporosis costs* were revised to include additional costs for an annual DEXA scan (£62) and prophylaxis medication (annual costs £296.40).

The ERG notes that the costs of osteoporosis are assumed to apply for the remainder of a patient's lifetime (or the model horizon). The ERG does not believe that DEXA scans would be undertaken repeatedly on an annual basis and notes that the annual costs proposed for prophylaxis medication were markedly higher than the average generic costs of oral therapies recently applied in NICE TA 464 (£296.40 vs £13.32).

The ERG incorporated additional adjustments assuming the costs of a one-time DEXA scan and using the annual average generic cost estimate for oral therapies of £13.32 reported in TA 464.

- *Diabetes costs* were inflated from 2005 to 2017 estimates.

The ERG considers this to be an appropriate adjustment and incorporated this in their revised results.

- *Fracture costs* were revised based on a targeted literature review and sourced from a reference specifically for patients 65-74 years old (Kanis et al 2007).

No details were provided on the targeted literature review and the reference provided was from 2007. The ERG revisions incorporated revised fracture costs consistent with those reported in TA 464.

- *Infection costs* were revised based on a targeted literature review. The company proposed higher estimates for some GC-related infections (Sarnes, 2011).

No details were provided on the targeted literature review or the specific basis for the alternative estimates. The ERG notes that the reference provided (Sarnes, 2011) is a US study and the generalisability of the findings to the NHS is unclear. In the absence of further evidence on the generalisability of this source, the ERG does not consider this to be an appropriate adjustment and no amendment is made in the revised ERG results.

Table 6 summarises the ICER results based on the ERG proposed revisions to the costs of GC-related AEs, incorporating previous corrections and amendments.

Table 6: ERG alternative (deterministic) ICER estimates incorporating revised GC-related AE costs and previous corrections and amendments

	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	8.72	[redacted]	10.78	7.17	-1.42	£3,856	0.00	0.15	£24,977
Tocilizumab with prednisone	7.30	[redacted]	10.78	7.32					

3.6 GCA relapse/flare amended to better reflect the GiACTA data

The company proposed a 10% adjustment to the relapse/flare rate estimates previously estimated by the ERG. The company stated that this provided a better estimate of the rate of flares in the control arm of the relapsed/refractory population.

No errors or uncertainties were identified regarding the ERG's previous approach. The ERG notes that the company estimates did not incorporate any new evidence and hence are unclear why any additional adjustment is necessary or appropriate. The ERG did not include the proposed revision in their revised base-case.

3.7 Revised ERG base-case results for 1-year tocilizumab treatment for relapsed/refractory GCA patients.

Table 7 and Table 8 summarise the ERG revised base-case results, combining all of the amendments considered appropriate by the ERG. The ERG's alternative estimates of the revised base-case ICER of 12 months tocilizumab treatment for relapsed/refractory GCA patients were £24,977 per QALY (deterministic estimate) and £24,032 per QALY (probabilistic estimate).

Table 7: ERG revised base-case (*deterministic*) results: 1-year treatment duration

	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	8.72	[redacted]	10.78	7.17	-1.42	£3,856	0.00	0.15	£24,977
Tocilizumab with prednisone	7.30	[redacted]	10.78	7.32					

Table 8 : ERG revised base-case (*probabilistic*) results: 1-year treatment duration

	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	8.54	[redacted]	10.56	7.01	-1.42	£3,743	0.00	0.16	£24,032
Tocilizumab with prednisone	7.12	[redacted]	10.56	7.16					

3.8 Areas of remaining uncertainty

Tocilizumab treatment duration

The ERG previously concluded that the 1-year treatment period results provided the most internally valid estimates consistent with the treatment duration period assessed in the GiACTA trial. However, uncertainty may remain concerning the extent to which this duration will be rigorously adhered to in clinical practice. The ERG also provided estimates of the revised base-case ICER for a 2-year treatment duration period for relapsed/refractory GCA patients.

Table 9 and Table 10 summarise the ERG revised base-case results, combining all of the amendments considered appropriate by the ERG for a 2-year treatment duration period. The ICER estimates were £55,924 per QALY (deterministic estimate) and £55,076 per QALY (probabilistic estimate).

The differences reported between the 1 and 2-year treatment duration periods clearly highlight the importance on ensuring that any potential guidance concerning shorter treatment duration periods are appropriately adhered to in clinical practice.

Table 9: **ERG revised base-case (*deterministic*) results: 2-year treatment duration**

	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	9.41	[redacted]	10.78	7.10	-2.23	£12,550	0.00	0.22	£55,924
Tocilizumab with prednisone	7.18	[redacted]	10.78	7.32					

Table 10: **ERG revised base-case (*probabilistic*) results: 2-year treatment duration**

	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	9.22	[redacted]	10.58	6.96	-2.17	£12,312	0.00	0.22	£55,706
Tocilizumab with prednisone	7.04	[redacted]	10.59	7.18					

GC-related disutility

A single GC-related disutility estimate (-0.07) was applied in the model based on an estimate reported by Niderkohr and Levin (2005). This study reported the annual incidence and disutility of GC-related adverse events based on a review of previously published studies. The single GC-related disutility estimate comprised a separate 'base' disutility estimate (-0.03) applied to all patients to represent a range of common side-effects of GCs (including weight gain, 'moon-shaped' facial appearance and frequent follow-up appointments) and additional disutilities for less common events including fracture, psychiatric disturbance and infections which were weighted according to their incidence.

In their response, the company noted that the published disutility estimate included a comprehensive but not exhaustive list of AEs that can result from steroid treatment. The company specifically noted that there were 2 well characterised steroid-related adverse events (depression and weight gain) that had not been incorporated into the cost-effectiveness model and hence the benefits of tocilizumab in limiting steroid exposure is plausibly underestimated.

The ERG acknowledges that the disutility estimate does not comprise an exhaustive list but considers the source to be the most relevant reference. The ERG is unclear about the specific concerns noted regarding the exclusion of depression and weight gain given that these appear to be captured in the 'base' utility estimate and the estimates for psychiatric disturbance.

The ERG previously raised uncertainties regarding the application of the single GC-related disutility estimate in the model. Specifically the assumptions concerning the 'base' disutility of -0.03 which is

included to capture a range of common side-effects of GCs (including weight gain, 'moon-shaped' facial appearance and frequent follow-up appointments) for all patients on steroids. The ERG noted that following a relapse/flare event, the GC-related disutility is applied during each cycle patients are in the subsequent remission state. This approach assumes that following a relapse/flare event, patients will continue to incur both the 'base' disutility and the specific side-effects for the remainder of their lifetime. The ERG concluded that it might not be appropriate to continue to apply the base-disutility (-0.03) unless patients continued to receive lifelong treatment with GC. This uncertainty was not addressed by the company in their response.

The ERG performed an additional exploratory analysis where the 'base' disutility was only applied for specific time periods (2 years, 5 years and 10 years). These time periods were used to proxy different fixed periods representing the alternative average durations of steroid treatment periods over a patient's lifetime.

Table 11 summarises the results of the ERG's exploratory analysis which is based on the ERG alternative base-case model previously reported in Table 7. The ERG notes that the ICER for tocilizumab falls below £30,000 per QALY when the average duration of steroid treatment over a patient's lifetime is assumed to be 5-years or more.

Table 11: ERG exploratory analysis for 'base' disutility

Steroid 'base' disutility – Two years	**Deterministic ICER**
One year tocilizumab treatment duration	£33,843
Two year tocilizumab treatment duration	£76,900
Steroid 'base' disutility – Five years	
One year tocilizumab treatment duration	£29,642
Two year tocilizumab treatment duration	£66,385
Steroid 'base' disutility – Ten years	
One year tocilizumab treatment duration	£27,077
Two year tocilizumab treatment duration	£60,106

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