Public observer slides

Tocilizumab for treating giant cell arteritis [ID1051] – STA

2nd Appraisal Committee meeting

Committee C, 23rd January 2018

Clinical effectiveness

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Tocilizumab (Roche)

Mechanism of action	Monoclonal antibody that inhibits interleukin-6, a cytokine that is partly responsible for inflammation of the arteries in giant cell arteritis
Marketing authorisation	Marketing authorisation for the treatment of giant cell arteritis in adults. There are no age restrictions.
Administration and dose	• 162 mg subcutaneous injection once per week in combination with a tapering course of glucocorticoids • Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice (as stated in Summary of Product Characteristics) • Monotherapy should not be used to treat acute relapses
Cost	• List price: £913.12 for 4 syringes containing 162 mg tocilizumab • A simple discount PAS price has been agreed with the Department of Health

Note: NHS England has a specialised commissioning policy for tocilizumab in GCA (July 2016) which does not commission tocilizumab. There is no NICE guidance.

Clinical pathway of care

All patients suspected of having GCA have steroid treatment:

- Initial dose is 60mg if there is vision loss, 40-60mg if not
- + tocilizumab?

Once symptoms of GCA are absent, the dose of steroids is tapered

- British Society for Rheumatology (BSR) suggests a regimen which lasts for a minimum of 52 weeks
- Company propose tocilizumab taken for 2 years and steroids tapered more rapidly

If patient relapses or 'flares':

- Steroid dose is increased and then tapered
- This can increase the duration of treatment and cumulative steroid dose substantially

Proposed benefits of tocilizumab:

- Reduce cumulative steroid dose and related adverse events through:

1) shorter tapering regimen and 2) lower relapse rate/longer remission reducing need for high steroid doses

ACD preliminary recommendation

Tocilizumab is not recommended for treating giant cell arteritis in adults

ACD committee conclusions (1)

Clinical need	• Valuable to have alternative treatment options that reduces flares of the disease and the cumulative amount of corticosteroids needed
Comparator	• Placebo

Trial data	• GiACTA study; weekly tocilizumab and placebo with 52-week prednisolone taper were most relevant. **However:**
	  • the taper period does not reflect clinical practice in England (it is usually over 18 – 24 months)
	  • the mean age of people with GCA is higher in the UK than those in the trial (73 vs. 69 years, respectively)
	• Subgroups in trial: Newly diagnosed and relapsing GCA

Effectiveness of tocilizumab	• For the overall population and both subgroups, tocilizumab plus corticosteroids is more effective than corticosteroids alone at:
	  • ↑ sustained remission at 52 weeks
	  • ↑ time to 1st flare
	• Results were similar between the subgroups

Adverse events	• Steroid related AEs were similar between arms (50% vs.49%) **but** because tocilizumab is taken with corticosteroids, the extent to which steroid-related AEs are reduced is unclear

ACD committee conclusions (2)

Utilities	• Agreed that the model adequately captures the negative impact of flares and corticosteroids on quality of life
Treatment duration	• **Uncertainty** with assuming that treatment with tocilizumab stops after 2 years • Average treatment would be at least 2 years and could be much longer • Tocilizumab may be re-started in the event of a flare up

Extrapolation of time to first flare	• Committee-preferred approach:
	  • treatment – Weibull
	  • comparator - exponential switching to Weibull after 2 years
	However, it may still be an overestimation of risk of flare in comparator arm because the extrapolation was based on the taper period, when the risk of flare is highest

Rate of subsequent flare	• Committee-preferred approach: using the probabilities of subsequent flares based on longitudinal cohort data (Labarca et al., 2016)
Results	• Plausible ICER for tocilizumab plus corticosteroids compared with corticosteroids alone (list price): £65,801 per QALY gained

ACD consultation responses

- **Consultee comments from:**
  - Roche (including additional evidence)
  - British Society of Rheumatology (BSR)
  - Royal College of Ophthalmologists (RCOPhth)
  - Vasculitis UK
  - Polymyalgia Rheumatica and Giant Cell Arteritis UK (PMRGCAUK)

- **Clinical Expert from:**
  - Justin Mason

- **Web comments from:**
  - 10 NHS professionals
  - 19 patients
  - 1 carer

British Society of Rheumatology (BSR)

- No clear distinction between different subgroups of GCA – tocilizumab would be most valuable for people with LV-GCA or relapsed/refractory GCA who can currently only be managed with long term steroid treatment. These people are:
  - more likely to have ↑ cumulative steroid burden, uncontrolled vascular inflammation and other steroid-related complications
- Tapering steroids alone may not be acceptable for all GCA people and steroids are not tapered to 0 in all GCA cases
- Not recommending tocilizumab may be viewed as a discrimination against older people and those who currently have no choice but to take long-term steroids for disease control
- GCA predominantly affects people aged 50+, who are in the greatest need of steroid-sparing medications due to high doses required and higher number of comorbidities
- For younger people with GCA, giving them high-doses of steroids puts them at high risk of a lifetime of significant disability and early unemployment
- For relapsed/refractory GCA, the disutility of steroid therapy is far higher than that used in the company model, which was mainly driven by risks of diabetes and fracture
- BSR would argue that the “52-week taper placebo arm” is not only 52-weeks of steroids tapering because the steroid dose was escalated in the event of relapse and therefore reflects current clinical practice in England
- Propose that people with steroid-related contraindications may be treated weekly with tocilizumab for 12 months along with steroid doses tapering to less than 5mg at around 6 months provided the disease is controlled

The Royal College of Ophthalmologists (RCOPhth)

The RCOPhth is concerned that the preliminary recommendation has not fully taken into consideration the following:

- Current difficulty in managing people with severe relapsing/refractory GCA
- People with GCA and have multiple-comorbidities, where treating with high dose steroids can be problematic and compound their existing premorbid conditions
- People with GCA are at higher risk of an excessive cumulative steroid dose due to multiple flares throughout their disease
- People with refractory/relapsing GCA will have higher cumulative steroid dose than people with uncomplicated GCA and therefore a higher risk of steroid-related AEs, but this has not been accounted for in the CE model
- The increased direct healthcare costs of refractory/relapsing disease, managing comorbidities and steroid toxicity or AE in GCA, including admitted patient care, out-patient care, primary care and emergency care, in some; and increased length of hospital stay have not been captured
- Patient voice from this disease group regarding their QoL and independence
- Not recommending tocilizumab could be seen as a discrimination against those who are of older age, where there has been little quality clinical data available

Vasculitis UK

- Steroid toxicity is the major hazard in the treatment of all types of vasculitis
- People with relapsed/refractory GCA, those who have experienced serious side-effects of long-term high steroid dose and those who with excessive cumulative dosage of steroids would particularly benefit from tocilizumab

Polymyalgia Rhuematica and Giant Cell Arteritis UK (PMRGCAUK)

- Unlike steroids, which work by controlling GCA symptoms, tocilizumab acts directly on the interleukin IL-6 to treat the disease. Hence, the assumption that tocilizumab is likely to be used for as long as steroid therapy alone is incorrect
- Consider it reasonable to prescribe tocilizumab to people with refractory GCA to reduce their dependency on steroids
- Tocilizumab has been recommended by the NHS England for a similar condition, Takiyasu's Arteritis, using evidence from GCA population
- There has been no significant advance in GCA treatment for over 60 years – prednisolone was first approved for clinical use in 1955
- The assumption that "most people with GCA" are in their 80s is incorrect:
  - there are many people with GCA in their 50s and 60s
  - the QALY calculations may therefore be skewed and should be revisited

ACD: *"[The committee] 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...The committee preferred the ERG's base case estimate, because it reflected some of its preferred assumptions. Specifically: the mean age was 73 years…"*

Clinical expert consultation response

- Concerned that the ICER for tocilizumab is so much higher than for the same drug for rheumatoid arthritis – questions how tocilizumab was modelled
- The importance of steroid-sparing effect of tocilizumab has not been fully considered in the ACD
- Tocilizumab would be most valuable for people with relapsed/refractory GCA
- Not recommending tocilizumab might significantly impact future clinical research in this area which has made no therapeutic progress for more than 50 years
- Although the duration of treatment may exceed 2 years for some people with GCA, this sample of people would be relatively small (~10-15%)

Patients and carers consultation response: Main themes

- GCA is an extremely debilitating disease that drastically affects QoL
- The age range assumption is incorrect: many people have GCA as early as in the 50s
- Currently no treatment plan for GCA, only control plan (steroids)
- Tocilizumab could:
  - help reduce the steroid dose and cumulative steroid burden as well as associated AEs and improve patient QoL
  - help people with GCA stop “yo-yoing” on steroid doses and eventually become drug-free
- Steroids alone is not sufficient in controlling pain and inflammation
- Older population should not be discriminated and denied a treatment that could potentially improve their QoL
- Cost may be a factor but patient perspective is equally important
- Tocilizumab has been recommended for a similar condition, Takiyasu’s Arteritis, using evidence from GCA population
- Tocilizumab is recommended for treating GCA in the USA and Canada, why not in England?

Healthcare professional (HCP) consultation response: Main themes

- 4 HCPs support the BSR response to NICE consultation for tocilizumab in GCA
- There is an unmet need for people with refractory/relapsing GCA:
  - long-term steroid doses is required in this population subgroup, increasing their risk of toxicity and serious drug-related AEs
  - there are more frequent outpatient appointments, telephone consultations and increased stress and anxiety
- People with GCA have no choice but to take high doses of steroids because there are no effective substitutes
  - Research shows that only a proportion of people have sustained remission on steroids alone -> a large proportion, especially the younger group 50+, will therefore have long-term negative impact on their QoL and ability to work
- 1 HCP with experience of using tocilizumab for GCP believe most people with GCA will do well with a decreasing dose of steroids over a period of 2 years
- 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 (n=1 HCP)

Company ACD consultation response
Burden on patients and the NHS and steroid burden

ACD: "*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.*"

Roche:

- The severity of GCA pathophysiology and the reduction in cumulative steroid burden have not been adequately reflected in the ACD
- Newly published literature (Dejaco et al. 2017; Mohammad et al. 2017; Kermani et al. 2017; Koster et al. 2018):
  - shows that vascular inflammation may lead to large-vessel complications such as arterial stenosis, vascular occlusion, myocardial infarction, aortic aneurysm, aortic dissection and upper limb ischaemia
  - confirms that underlying co-morbidities are more common in people with GCA than reference populations, including cardiovascular diseases, rheumatologic diseases, osteoporosis, severe infections and diabetes
- The 2017 CPRD analysis reports that hospitalisation rates among GCA patients are significantly ↑ vs. matched controls (Incidence Rate Ratio 1.7 95% CI 1.6 – 1.8)

ERG critique: No new significant evidence reported. Evidence from new source (Mohammad et al. 2017) is consistent with previously considered evidence

Company ACD consultation response
Identifying the greatest unmet need

ACD: *"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."*

Roche:

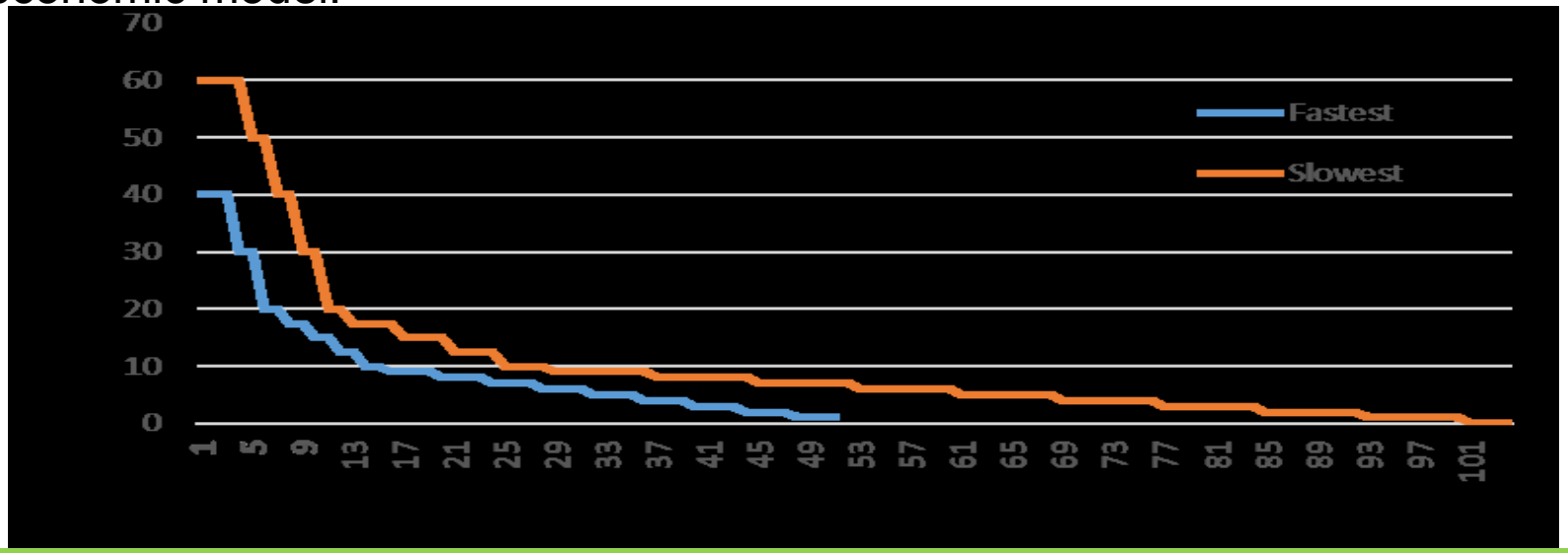
- Agrees that tocilizumab would be most valuable for people with relapsed/refractory GCA but considers that the rationale for this has not been fully explained in the ACD
- Relapsed/refractory (R/R) patients are likely to have sub-optimally treated disease, by definition; pre-existing high cumulative steroid burden; greater concomitant medication usage; higher body weight; and/or greater burden of comorbidities
- Subgroup analysis for the relapsed/refractory population was previously provided and results were discussed at the ACM1 but not reported in the ACD
- Agrees that there may be other relevant subgroups but robust evidence is lacking due to small population numbers

→ Because people with relapsed/refractory GCA have the highest unmet need, the revised CE model is targeted to relapse/refractory GCA people

Company ACD consultation response
Current standard of care: steroid tapering regimens

Roche:

- Agrees that tapering steroids over 52 weeks in the corticosteroids-only arm, which is the "fastest" possible BSR recommended regimen, may not reflect current clinical practice in the NHS
- A longer ("slowest") BSR recommended tapering regimen (assuming no GCA relapse) is therefore adopted and this has been incorporated into the amended economic model:



ERG critique: Only the cost of the comparator steroid-taper regimen is adjusted, no adjustment is made to the clinical efficacy data → uncertainties regarding the possible impact on the number of flares and time to first flare still remain.

Company ACD consultation response
GiACTA baseline remission status

ACD: *"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".*

- **Roche:** A new exploratory analysis showed no difference in primary endpoint when analysed by remission status at baseline:

	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

ERG critique:
- The company has not provided any statistical tests to support their conclusion
- The evidence does not negate the concerns of possible bias as fewer people in the comparator arm who were not in remission at baseline achieved sustained remission at 52 weeks vs. people who were in remission at baseline

Company ACD consultation response:
Steroid-related adverse events

ACD: *"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."*

Roche:

- The ACD understates the serious consequences of the high cumulative steroid burden suffered by GCA patients
- Provides published evidence which outlines:
  - the rate at which patients might experience additional steroid-related adverse events
  - the correlation between increasing harm and increasing average daily dose and cumulative dose
  - EULAR taskforce recommends that at ≤5 mg/day steroids there is an acceptably low level of harm
- Steroid-related AEs costs have been updated in the revised CE model to reflect 2017 health care resource use

ERG critique: No new significant evidence reported. Evidence from new sources is consistent with previously reported evidence in the company submission

Company ACD consultation response
Clinical effectiveness of tocilizumab: Impact on steroid-related toxicities (1)

ACD: *"Because tocilizumab is taken with corticosteroids, the extent to which steroid-related adverse events are reduced is unclear"*

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
- As shown in a recent retrospective study (Broder et al., 2016), there is a 3% increase in relative risk of AEs with each gram of cumulative steroid
- People on tocilizumab can taper to zero steroid within 6 months, after which they are managed on tocilizumab monotherapy – this is supported by clinical experts and is in alignment with the results in GiACTA

Company ACD consultation response
Clinical effectiveness of tocilizumab: Impact on steroid-related toxicities (2)

ACD: *"median cumulative steroid dose was lower in the tocilizumab arm of GiACTA, but noted that this was over the relatively short 52-week follow-up.. [The committee] 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%)"*

Roche:

- GiACTA was not designed to determine the long-term steroid-sparing benefits of tocilizumab, or the safety related to steroid use
- Many steroid-related AEs manifest in the longer-term, hence no significant differences were expected over the course of the 52-week study
- To confirm which AEs in GiACTA could be considered related to steroid use, Roche conducted a new post-hoc analysis

	PBO+52	TCZ QW
Steroid-induced toxicity	[redacted]%	[redacted]%

- In addition, published evidence has proven that steroids are clearly associated with a range of SAEs (see slides 15-17)

ERG critique: Impact on steroid-related toxicities

- The company does not provide any statistical test to support the difference in steroid-related toxicity between arms in the post-hoc analyses
- Data were analysed retrospectively and not based on standard or pre-specified criteria
- CEM incorporates external data on the relationship between cumulative steroid dose and steroid-related AEs → the potential impact has therefore already been quantified

Company ACD consultation response

Duration of tocilizumab treatment

Roche disagrees with the Committee that all patients would need to be treated with tocilizumab for 2 years or more

ACD: *"The company assumed in their economic model that treatment with tocilizumab stops after 2 years. However, the committee was concerned the 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 "*

Roche:

- Roche and clinical experts consider that 12 months tocilizumab treatment would provide clinically relevant efficacy and be a responsible use of NHS resources
- Part 2 follow-up GiACTA - 1 year of treatment with tocilizumab is sufficient to sustain remission long-term: [redacted]% of those on TOC QW tocilizumab remained in sustained remission after stopping treatment and had reached study week ≥100
- In a new review of published case series (n=109 people with GCA), the majority of people also received tocilizumab for less than 1 year (range 1 to 53 months)
- For people who are unable to taper to 0mg steroid in 52 weeks, expert clinicians and international clinical guidelines agree 5-7.5mg/day to be an acceptable maintenance dose
- 1 year treatment duration is incorporated into the revised economic model

ERG critique: Duration of tocilizumab treatment

- No details of follow-up times or planned duration of tocilizumab treatment were provided for majority of the case reports (follow-up time was only reported for Regent et al., 2016))
  - Follow-up completeness is necessary for reliable outcome assessment and credibility of evidence
- Case reports are a lower level of evidence with less validity than RCTs
- 1-year is most internally valid but there may be implementation issues

→ Not sufficient information provided to fully address the uncertainties around duration of tocilizumab treatment

Company new evidence:
Revision of the cost-effectiveness model

- The company's revised CE model is targeted to relapse/refractory GCA people with a 12 month treatment duration
- ERGs model and preferred assumptions were used
- In addition, the following changes to the revised CE model were made:

1. Correcting 2 errors in the model:
   - The annual concomitant medication costs applied to placebo arm
   - Using average weight of the GiACTA relapsing/refractory population instead of the UK population to calculate the dosages of concomitant medication
2. Incorporating the slowest steroid taper regimen in the prednisolone-only arm
3. Incorporating the costs for Accident and Emergency visits, which were combined with visits to "other" clinicians in the original model, costed at a lower rate (£164 vs. £1,006 per visit)
4. Updating the costs of steroid-related AEs to 2017
5. Applying a 10% adjustment to the ERG's flare rate (based on Labarca 2016). This is to account for the incremental difference observed between the ITT and the relapsed/refractory population in the prednisolone arm

Company new evidence: Revised company base case (with PAS)

Treatment (12 mth R/R)	QALYs	Incr. QALYs	Costs	Incr. costs	ICER
1. Amended model errors					
Prednisone	7.17	0.15	£[redacted]	£4,003	£25,929
TOC with prednisone	7.32		£[redacted]		
2. 'Slowest' BSR recommended tapering regimen (1-2 combined)					
Prednisone	7.17	0.15	£[redacted]	£3,707	£24,008
TOC with prednisone	7.32		£[redacted]		
3. A&E visits currently occurring in the NHS for GCA patients (1-3 combined)					
Prednisone	7.17	0.15	£[redacted]	£3,590	£23,244
TOC with prednisone	7.32		£[redacted]		
4. Incorporating costs published in relation to steroid-related AEs (1-4 combined)					
Prednisone	7.17	0.15	£[redacted]	£3,002	£19,348
TOC with prednisone	7.32		£[redacted]		
5. Amended flare rate for relapsed/refractory patients receiving placebo (1-5 combined)					
Prednisone	7.16	0.16	£[redacted]	£2,959	**£18,801**
TOC with prednisone	7.31		£[redacted]		

Company new evidence: Uncertainties in the model

Roche:

- Not all cost and utility evidence can be incorporated due to lack of evidence:
  - Only costs for steroid burden AEs in CPRD analysis are included
  - Not all GCA-related complications included (in particular, depression and weight gain)
  - Not all costs of flare avoidance included

ERG: Acknowledges that the disutility estimate does not comprise an exhaustive list but is the most relevant reference. Depression and weight gain are already captured in the "base" utility estimate and the estimates for psychiatric disturbance.

Roche:

- The PSSRU reports separate costs for "high-costs patients discharged from Acute Medical Unit (top 25% of most costly patients)" – if applied to all GCA patients, the deterministic ICER for 12 months tocilizumab in relapsed/refractory people would be £4,065/QALY gained

ERG: No comments.

ERG critique: Company's revision of the cost-effectiveness model (1)

Revised company base case assumptions	ERG critique
Focused on 12 months tocilizumab treatment for R/R only	• No new evidence used to inform the clinical efficacy assumptions applied within the revised model
Correcting 2 errors in the CEM: a. Concomitant medication costs in placebo arm b. Using average weight of the GiACTA (R/R) population to calculate dosages of concomitant medication	a. ERG agrees this is a programming error. However, the revisions did not account for mortality b. Using weight estimates of the R/R population is appropriate but body surface area estimates should also be altered to be consistent → ERG's proposed revisions account for mortality and include adjustments for both weight and BSA estimates
Incorporating the slowest steroid taper regimen in the prednisolone-only arm	ERG does not agree with the company's proposed amendment • Only the cost of the comparator steroid-taper regimen is adjusted - uncertainties regarding the impact on clinical efficacy remain

ERG critique: Company's revision of the cost-effectiveness model (2)

Revised company base case assumption	ERG critique
Incorporating the costs for Accident and Emergency (A&E) visits (£1,006/visit)	• Company's revised unit cost estimate for A&E visits refers to a combined estimate of the annual cost of A&E and outpatient care → ERG proposes an alternative estimate based on NHS reference costs: £146.86
Updating the costs of steroid-related AEs to 2017: ▪ Osteoporosis costs: annual DEXA scans and prophylaxis medication costs ▪ Diabetes costs: inflated from 2005 to 2017 estimates	Osteoporosis costs: • DEXA scans would be undertaken on an annual basis and the annual costs of prophylaxis were much higher than the average generic costs of oral therapies applied in NICE TA464 (£296.40 vs. £13.32) → ERG proposes assuming the costs of a one-time DEXA scan and using average generic cost estimate for oral therapies (from TA464) Diabetes costs: ERG considers this to be an appropriate adjustment

ERG critique: Company's revision of the cost-effectiveness model (3)

Revised company base case assumption	ERG critique
Updating the costs of steroid-related AEs to 2017 (continued): ▪ Fracture costs: revised based on a targeted literature review and sourced from Kanis et al. ▪ Infection costs: revised based on a targeted literature review. The company proposed higher estimates for some GC-related infections (Sarnes, 2011)	Fracture costs: • No details provided on the targeted literature review and the references provided was from 2007 → ERG proposes alternative estimates consistent with those used in TA464 Infection costs: • No details provided on the targeted literature review • Sarnes (2011) is a US study and generalisability of the findings to the NHS is unclear → ERG does not consider this to be an appropriate adjustment
Applying a 10% adjustment to the ERG's flare rate	• No new evidence to support the need for company's proposed additional adjustment → ERG does not consider this to be an appropriate adjustment

ERG revised alternative (deterministic) ICER estimates (with PAS)

	Incr. Flares	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1. ERG alternative ICER estimates incorporating proposed corrections					
Prednisone alone	-1.42	£4,159	0.00	0.15	**£26,938**
Tocilizumab + prednisone					
2. ERG alternative ICER estimates incorporating revised unit costs for Accident and Emergency visits and previous corrections (1-2 combined)					
Prednisone alone	-1.42	£4,161	0.00	0.15	**£26,951**
Tocilizumab + prednisone					
3. ERG alternative ICER estimates incorporating revised GC-related AE costs and previous corrections and amendments (1-3 combined)					
Prednisone alone	-1.42	£3,856	0.00	0.15	**£24,977**
Tocilizumab + prednisone					

ERG revised alternative base-case results: 1 year treatment duration (with PAS)

ERG's revised base case incorporates all amendments considered appropriate by the ERG (corrections to the model, revised unit costs for A&E visits and revised GC-related AE costs)

	Total Flares	Total costs	Total LYG	Total QALYs	Incr. Flares	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Deterministic									
Prednisone alone	8.72	£[redacted]	10.78	7.17	-1.42	£3,856	0.00	0.15	**£24,977**
Tocilizumab + prednisone	7.30	£[redacted]	10.78	7.32					
Probabilistic									
Prednisone alone	8.54	£[redacted]	10.56	7.01	-1.42	£3,743	0.00	0.16	**£24,032**
Tocilizumab + prednisone	7.12	£[redacted]	10.56	7.16					

ERG revised alternative base-case results: 2 year treatment duration (with PAS)

ERG's revised base case incorporates all amendments considered appropriate by the ERG (corrections to the model, revised unit costs for A&E visits and revised GC-related AE costs)

	Total Flares	Total costs	Total LYG	Total QALYs	Incr. Flares	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Deterministic									
Prednisone alone	9.41	£[redacted]	10.78	7.10	-2.23	£12,550	0.00	0.22	**£55,924**
Tocilizumab + prednisone	7.18	£[redacted]	10.78	7.32					
Probabilistic									
Prednisone alone	9.22	£[redacted]	10.58	6.96	-2.17	£12,312	0.00	0.22	**£55,706**
Tocilizumab + prednisone	7.04	£[redacted]	10.59	7.18					

ERG exploratory analysis: GC-related disutility

- Uncertainties regarding the assumptions about the separate "base" disutility of -0.03, which is included to capture common side-effects of GCs for all people on steroids:
  - Applied during each cycle people are in the subsequent remission state following a relapse/flare **->** assumes people will continue to incur both the "base" disutility and the specific side-effects for the remainder of their lifetime – *plausible*?
- ERG's exploratory analysis: "base" disutility was only applied for specific time periods (2 years, 5 years and 10 years), representing alternative average durations of steroid treatment periods over a person's lifetime

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 year	
• One year tocilizumab treatment duration	£27,077
• Two year tocilizumab treatment duration	£60,106

Issues for consideration

- Should the risk and impact of steroid-related AEs in people with GCA be re-considered? Has the perspective of people with GCA been fully considered? Should these be re-worded?
- Does the committee accept:
  - the relapsed/refractory GCA sub-group analysis
  - duration of tocilizumab treatment (12 months)
  - amended model errors
  - 'slowest' BSR recommended tapering regimen
  - incorporating the new costs for A&E visits
  - updating the costs of steroid-related AEs to 2017
  - applying a 10% adjustment to the ERG's flare rate
- What is the most plausible ICER?
- Is there an equality issue related to age if tocilizumab is not recommended?