NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tocilizumab for treating giant cell arteritis

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tocilizumab for treating giant cell arteritis ID1051

Contents:

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

Pre-meeting briefing

Tocilizumab for treating giant cell arteritis

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

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

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the committee meeting

1

Key clinical issues

- Are the GiACTA trial results generalisable to NHS clinical practice?
  - small number of UK patients, lower mean age, high proportion of large vessel disease
  - 52 week tapering regimen shorter than ~2 years reported in clinical practice – relapse rates associated with tapering regimen
- Are the results likely to be biased in favour of tocilizumab because not all patients were in remission at the start of the trial (and the start of the tapering regimen)?
- Should the newly diagnosed and relapsing subgroups be considered separately?

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Key cost effectiveness issues (1)

- How should time to first flare be extrapolated?
  - Company's extrapolation assumes constant benefit of tocilizumab over prednisolone regardless of duration of treatment
  - ERG suggests more appropriate to use same distribution after 2 years, either:
    - 1a) exponential as company used for prednisolone alone, but this predicts high number of relapses for both treatments
    - 1b) Weibull as company use for tocilizumab
  - ERG suggests Weibull is appropriate, as:
    - assumes declining risk over time, in line with epidemiological data
    - estimate of people not relapsed at 5 years more externally valid
    - fits tocilizumab arm best, which is based on more data than prednisolone

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Key cost effectiveness issues (2)

- How should rate of subsequent flare be modelled?
  - company estimates higher probability of subsequent flares for newly diagnosed population than relapsing population (tocilizumab arm) and high mean number of flares over model time horizon
  - ERG estimates logically consistent probabilities across subgroups and predicts a lower mean number of flares, in line with external data
- What is the most appropriate tocilizumab treatment duration?
  - company and ERG base cases assume 2 years, with scenarios assuming 1 year
  - 1 year is most internally valid estimate, consistent with treatment duration in GiACTA, but 2 years may be more externally valid
  - preliminary results of long term follow-up data suggests for sustained benefit, significant proportion of people need continued treatment
- What are the most plausible ICERs?
- Are there any additional benefits that have not been captured in the QALY calculation?

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Disease background

- Giant cell arteritis (GCA) causes inflammation in the walls of arteries, usually in the head and neck (cranial GCA) and less commonly the aorta (large vessel GCA)
- Inflammation causes the arteries to narrow, restricting blood flow
- Cause is unknown, but has been linked to genetic factors, infection, or history of cardiovascular disease
- Complications include permanent vision loss, stroke and aortic aneurysm
- It affects 1 in every 4,500 people aged over 40 years annually in the UK. It is rare in people aged below 50 years and the risk increases with age
- Cranial GCA generally has shorter disease duration (1-2 years) and fewer relapses than large vessel GCA
- Main aim of treatment is to control symptoms, reduce inflammation and reduce risk of complications
- Initial treatment is with high-dose corticosteroids, such as prednisolone which is gradually reduced – 'tapered' – over a period of 18 to 24 months

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Impact on patients and carers

- First symptoms may be unexpected loss of sight in one or both eyes
- Ongoing effects include headaches, jaw pain, fever, fatigue, muscle and joint pain and weight loss
- Symptoms can have a cumulative effect on mental health
- While incidence is highest in 80+ age group, a significant number of people in the 50 to 60 age group have the disease
  - these people may have many years of symptoms and side effects of current treatments
- Reduction in patient's health, especially mobility problems may have an impact on carers who are likely to be similar age
- Patient group feels this disease area has received little attention

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Patient organisation views

- Current long-term treatment with steroids can have serious side effects such as diabetes, osteoporosis and cataracts
  - population already likely to have other health conditions because of age
- Steroid treatment can increases risk of cardiovascular and cerebrovascular events – which reduces quality of life
- Treatment of side effects of steroids has significant health costs
- Tocilizumab treatment would reduce need for long-term steroids, so reduce side-effects and also reduce risk of relapse

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Clinical expert and professional organisation views

- Innovative treatment – 1st advance in management of GCA for 60 years
- Unmet need for targeted treatment that reduce cumulative steroid dose
- Anticipated benefits:
  - greatly reduced use of steroids with consequent reduction in side effects
  - reduced risk of relapse
  - long term remission and freedom from the need for active treatment
- Greatest potential impact for:
  - newly diagnosed people for whom steroid treatments are contraindicated e.g. because of type 2 diabetes, congestive cardiac failure, steroid psychosis
  - people whose disease relapses on doses of steroids greater than 15mg or who are suffering with significant complications of steroid treatment
- Patients may find weekly subcutaneous injection preferable to managing a course of tapering steroids
- No guidelines or evidence as to when tocilizumab treatment could be withdrawn, but perhaps after 18-24 months

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Tocilizumab (RoActemra, 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
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 • Cost of a course of treatment (assumed by the company to be 2 years): [redacted] (including agreed patient access scheme)

Note: NHS England has a specialised commissioning policy for tocilizumab in GCA (July 2016) which does not commission tocilizumab

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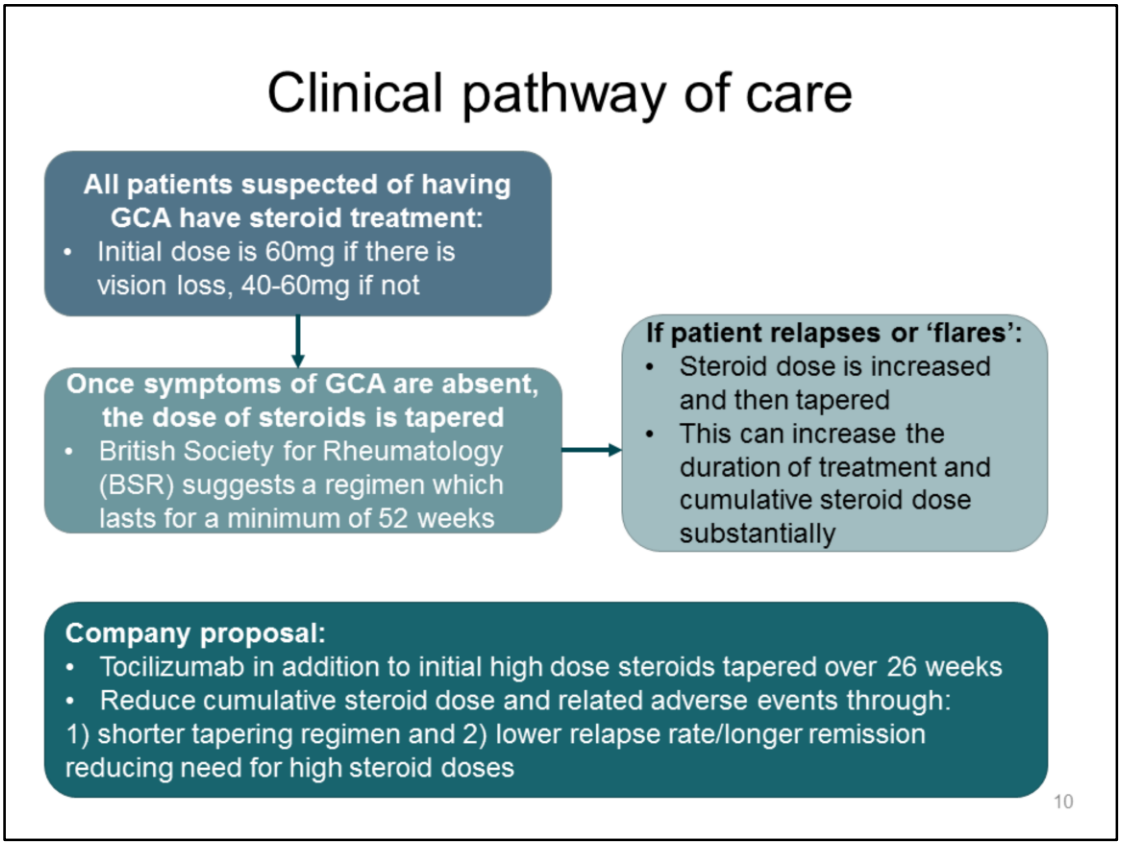
- Marketing authorisation for GCA is an extension to the existing marketing authorisation for rheumatoid arthritis and juvenile idiopathic arthritis
- There is existing NICE Technology Appraisal guidance for the rheumatoid arthritis and juvenile idiopathic arthritis indications
- Company provide a homecare delivery and healthcare service see slide 31 for more details



- There is no NICE guidance or pathway for GCA
- NHS England (2016) Clinical Commissioning Policy: Tocilizumab for Giant Cell Arteritis (adults)
- British Society for Rheumatology guidelines: https://www.ncbi.nlm.nih.gov/pubmed/20371504

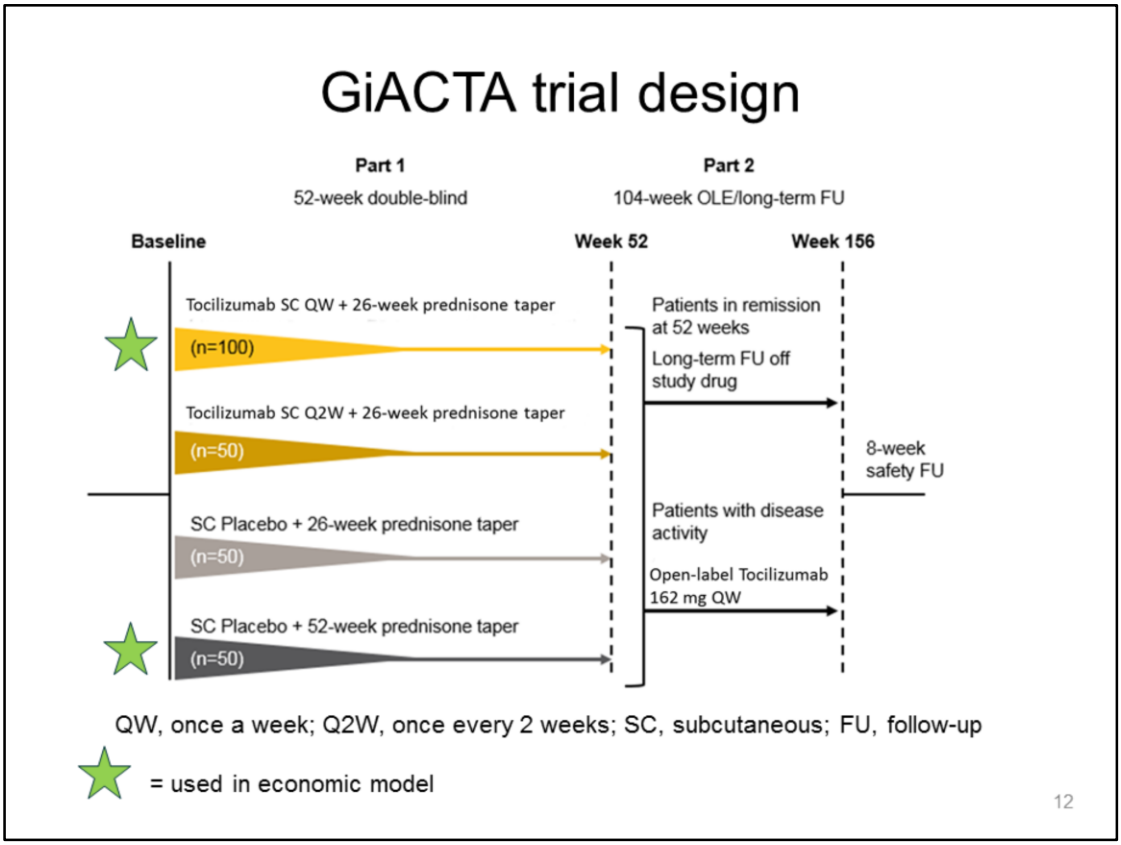
ERG report page 24:

- At least 50% of GCA patients relapse during steroid tapering, but relapses are rare when dose >20mg daily
- Majority of relapses are associated with rapid steroid tapering

Trial evidence – GiACTA trial

Description	• Phase III, multicentre, double-blind, placebo-controlled study • Randomisation stratified by baseline steroid dose (≤30 or >30 mg per day) • Pre-planned subgroups: newly diagnosed and relapsing patients • 6 week screening phase in which flare was managed with steroids, with the aim of achieving remission by the trial baseline
Eligibility criteria	• Aged ≥50 years • New-onset GCA (diagnosed <6 weeks before baseline visit) or, • Relapsing GCA (diagnosed >6 weeks before baseline visit and previous treatment with ≥40 mg/day corticosteroids for ≥2 consecutive weeks) • Active disease within 6 weeks of baseline visit
Permitted concomitant medications	• Short-term steroids could be administered in addition to the protocol-defined taper regimen • Methotrexate: the dose was to remain stable and not be increased. The dose could be reduced or discontinued if necessary for safety reasons
Outcomes	1º: proportion of patients in sustained remission at Week 52 2º: time to flare after disease remission, health-related quality-of-life

- For primary outcome to be met, remission had be sustained from week 12 to 52
- Remission was defined as the absence of flare (see below) and normalization of C-reactive protein (CRP < 1 mg/dL)
- Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or erythrocyte sedimentation rate ≥ 30 mm/h attributable to GCA



Source: company submission figure 2

Rationale for choice of arm used in submission and economic model:

- Tocilizumab once weekly matches the marketing authorisation
- Placebo+52 week steroid taper matches minimum recommendation in British Society for Rheumatology guidelines

Baseline characteristics

	Tocilizumab (weekly) + 26 week steroid taper n=100	Placebo + 52 week steroid taper n=51
Age, years, mean (SD)	69.5 (8.5)	67.8 (7.7)
Female, %	78	73
Ethnicity: white, %	97	96
Newly diagnosed GCA ,%	47	45
Relapsing GCA, %	53	55
Baseline prednisone dose, % ≤30 mg/day >30 mg/day	 52 48	 51 49
Disease duration, days, mean	306.8	255.2
Signs or symptoms of GCA, %	37	47
Erythrocyte sedimentation rate, mm/h, mean (SD)	24.6 (18.7)	24.2 (18.2)
Diagnosis: positive temporal artery biopsy, %	57	57
Diagnosis: positive imaging, %	50	45
In remission at baseline, %	55	51

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Source: company submission table 7
Signs and symptoms of GCA: new-onset localised headache, scalp tenderness, or temporal artery tenderness, decreased pulsation, or jaw or mouth claudication.

ERG comments on trial

- Prednisolone used in NHS rather than prednisone, but they are highly comparable, prednisone being metabolic precursor of prednisolone
- Not all patients were in remission at baseline (49% placebo+52 week taper, 45% tocilizumab), but all patients had to start the tapering protocol
  - patients not in remission and receiving placebo only may bias results in favour of tocilizumab
- 17% of overall population have steroid refractory GCA (never achieved remission with steroids) but proportion not reported by treatment arm
- There are a number of imbalances in the reported baseline characteristics between the treatment groups, but the differences generally balance out, with no obvious skew
- Only 7 patients in once weekly tocilizumab arm from UK
- Baseline characteristics reflect the population seen in clinical practice
  - exceptions are lower mean age in trial (69 years vs. 73 years in UK Clinical Practice Research Datalink [CPRD]) and a potential overrepresentation of large vessel GCA (40% vs. ~5%)

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- ERG report page 26: high number with large vessel disease may relate in part to differences in the availability of vascular imaging in the UK versus countries where services operate on a fee-for-service model
- Vascular imaging, is more effective in diagnosing large vessel GCA patients. Therefore, the rates of large vessel GCA in the UK may be under estimated

GiACTA trial results – overall population

	Tocilizumab (weekly) + 26 week steroid taper n=100	Placebo + 52 week steroid taper n=51
Sustained remission at week 52	56.0%	17.6%
Unadjusted difference (99.5% confidence interval)	38.4% (17.89 to 58.81), p<0.0001	
Flare by week 52	23%	49%
Time to first flare: median	Not evaluable	295 days
Time to first flare: hazard ratio (99% confidence interval)	0.39 (0.18 to 0.82), p=0.0011	
Annualised relapse rate: mean	0.41	1.30
Annualised relapse rate: range	0 to 4.0	0 to 10.3
Cumulative steroid dose: median (95% confidence interval)	1,862 mg (1,582 to 1,942)	3,818 mg (2,818 to 4,426)
	p<0.0001	

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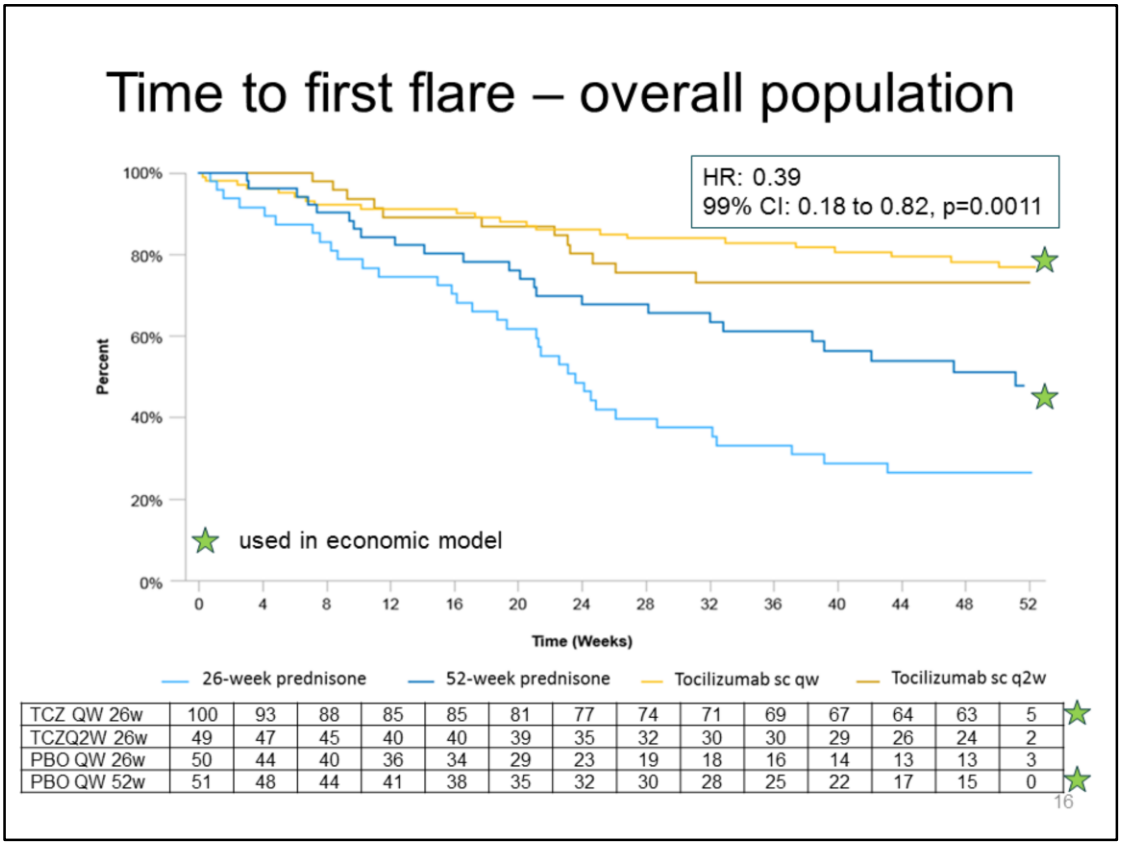
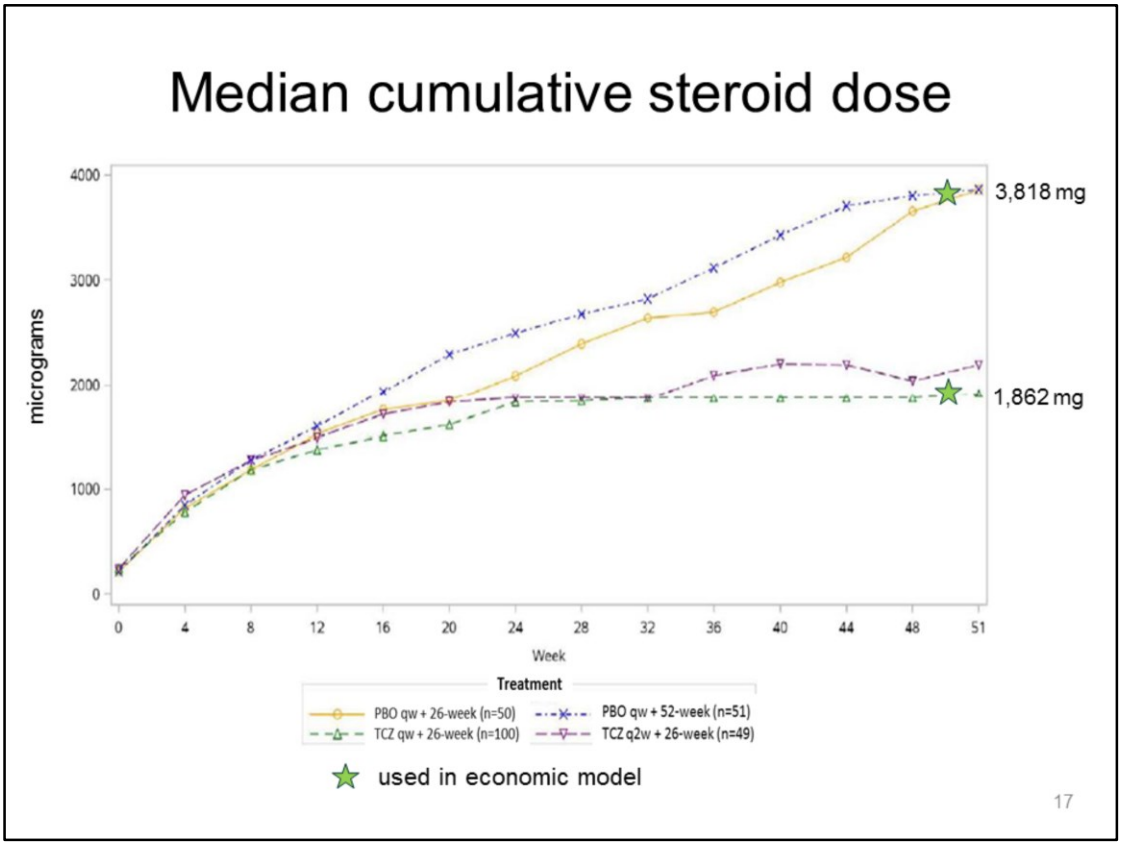
Source: company submission tables 11, 12, 13, 14



Source: company submission figure 3



Source: company submission figure 4

GiACTA trial results – subgroups

Main differences in baseline characteristics:

- Median starting steroid dose ≥60mg/day: newly diagnosed, 18%; relapsing, 5%
- In remission at baseline: newly diagnosed, 71%; relapsing, 46%

	Newly diagnosed patients		Relapsing patients	
	Tocilizumab +26wk taper n=47	**Placebo + 52wk taper n=23**	**Tocilizumab +26wk taper n=53**	**Placebo + 52wk taper n=28**
Sustained remission at week 52	59.6%	21.7%	52.8%	14.3%
Unadjusted difference	37.9%		38.5%	
Time to first flare: median	Not evaluable	Not evaluable	Not evaluable	274 days
Time to first flare: HR (99% CI)	0.44 (0.14 to 1.32)		0.36 (0.13 to 1.00)	
Cumulative steroid dose: median (95% CI)	1,942 mg (1,822 to 2,519)	3,817 mg (2,578 to 4,585)	1,385 mg (1,127 to 1,862)	3,785 mg (2,223 to 5,373)

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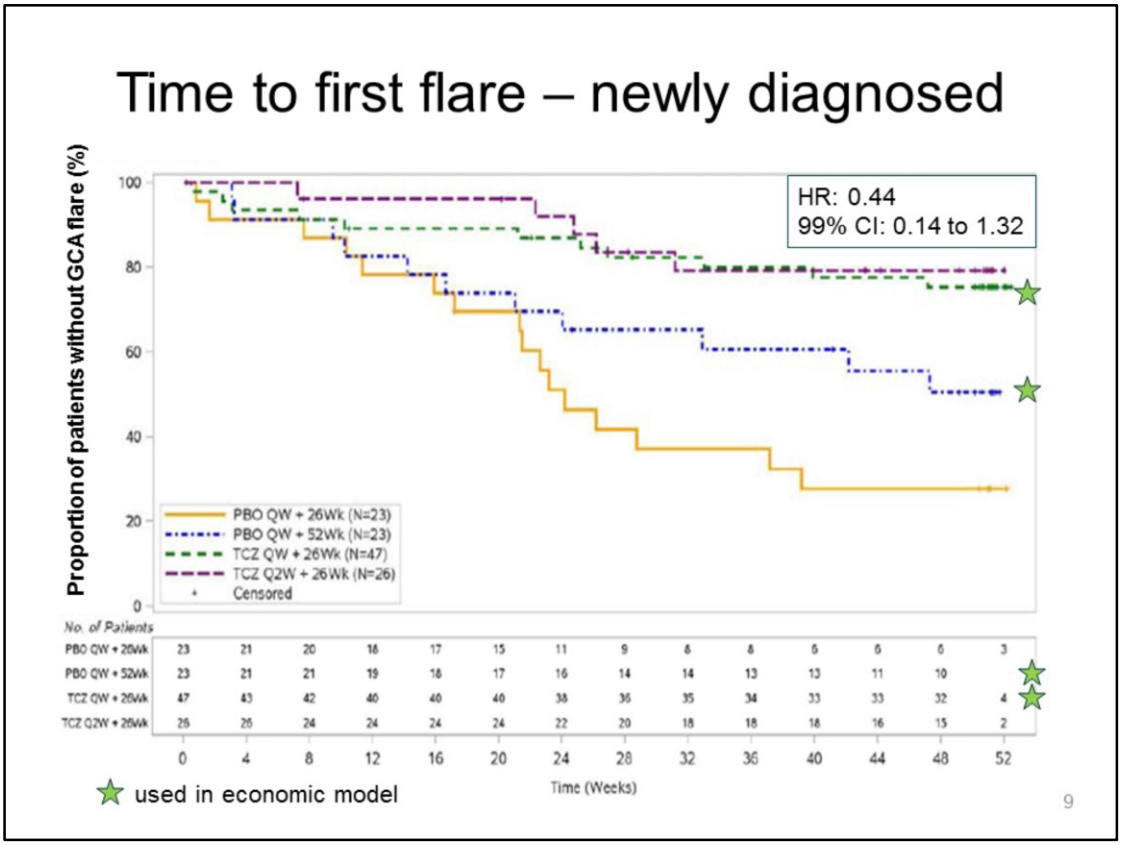
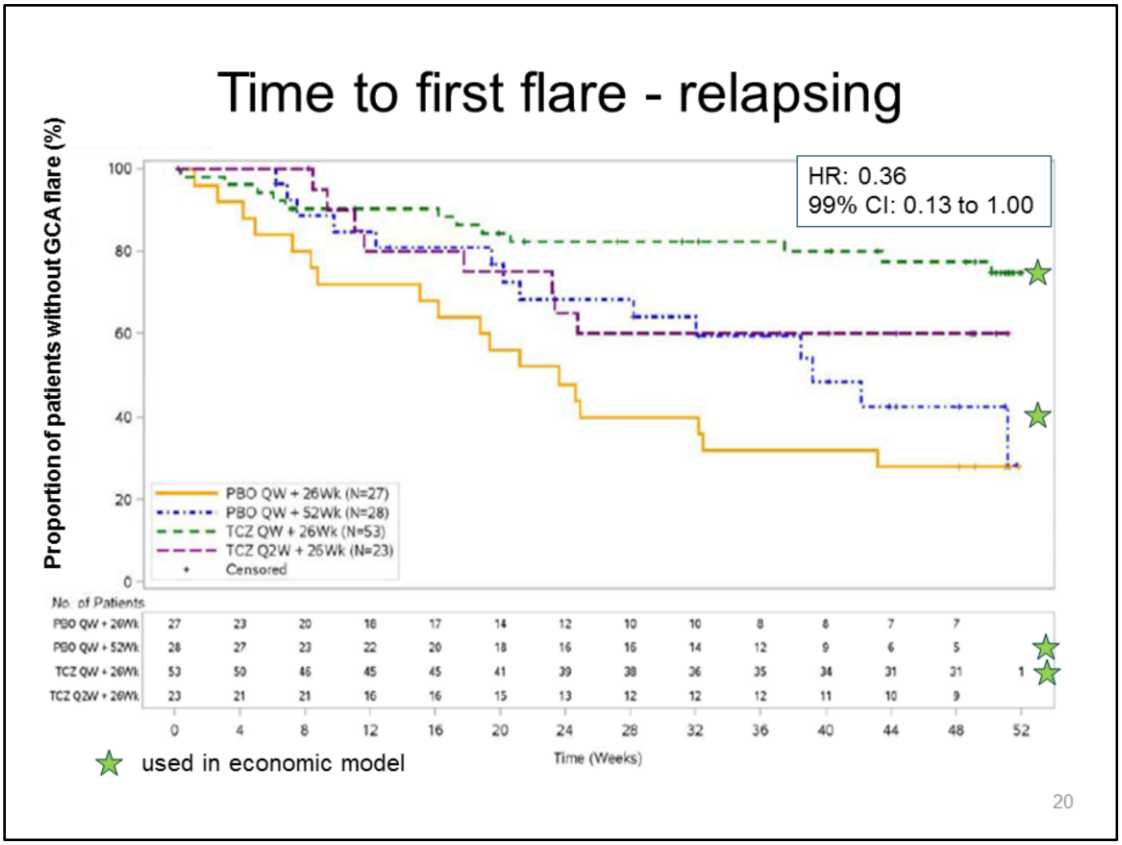
Sources: baseline characteristics source, ERG report page 44; results, company submission appendix E and ERG report page 47 (superseded by erratum)



Source: company submission figure 5, appendix E



Source: company submission figure 6, appendix E

Longer term disease control

- Part 2 of the GiACTA trial is an ongoing open-label extension, following patients for an additional 2 years
- Patients in remission at week 52 stop taking tocilizumab and the duration of response enabled by 1 year of tocilizumab treatment is assessed
- 35 patients treated with tocilizumab (either weekly or fortnightly) had a sustained remission (from 12 to 52 weeks) at the end of the trial
  - of these, 16 (46%) experienced a flare in part 2 of the trial (33% in weekly tocilizumab group)
  - [redacted]
  - [redacted]
- **Treatment duration:** Clinical experts: no guidelines or evidence as to when tocilizumab treatment could be withdrawn, but perhaps after 18-24 months
- Not clear in clinical practice if tocilizumab treatment would stop at 52 weeks, given that risk of relapse remains

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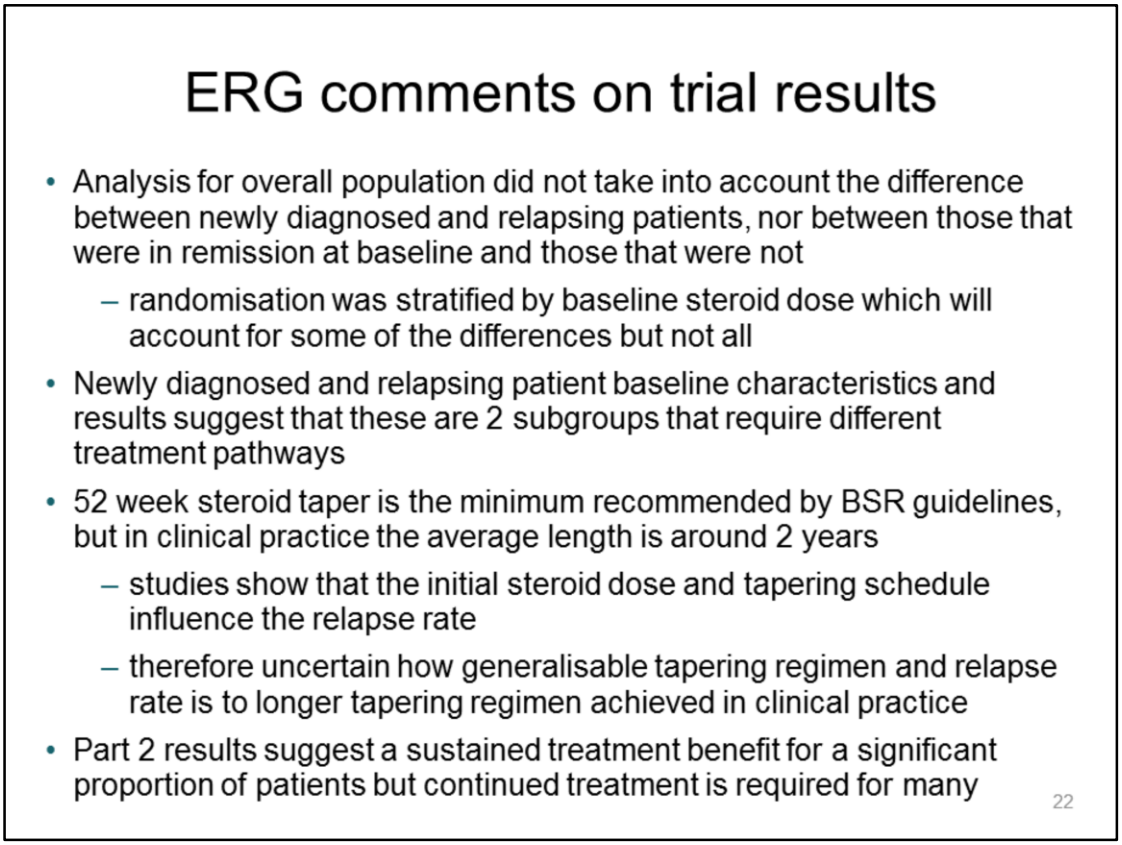

Page 32 ERG report:
ERG is uncertain whether newly diagnosed and relapsing patients would be treated similarly in clinical practice:

- Clinical advice is that patients with newly diagnosed GCA generally have a better outcome from steroid treatment than patients with relapsing GCA
- Patients with relapsing GCA already have the burden of previous steroid treatment with its cumulative toxicity, meaning that clinicians may be reluctant to go straight to the highest doses; and after initial response to steroids relapsing patients are then more likely to flare again during tapering, because patients who have flared once are more likely to flare again subsequently.
- Therefore, tocilizumab may be more beneficial in patients with relapsing GCA who have previously been exposed to steroid treatment.
- However, newly diagnosed patients who have experienced adverse effects from steroids or are at high risk of mental health problems would benefit from tocilizumab treatment and lower cumulative doses of steroids.

Adverse events

	Tocilizumab (weekly) + 26 week steroid taper	Placebo + 52 week steroid taper
Proportion with at least 1 adverse event	98%	92%
Serious adverse event	15%	26%
Most common adverse event: infection/infestation	75%	65%
-serious infections	7%	12%
Adverse event leading to withdrawal from treatment	11%	0%
Steroid related adverse event	50%	49%
-serious steroid related adverse events	3%	8%

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Source: company submission tables 21 and 22

Key clinical issues

- Are the GiACTA trial results generalisable to NHS clinical practice?
  - small number of UK patients, lower mean age, high proportion of large vessel disease
  - 52 week tapering regimen shorter than ~2 years reported in clinical practice – relapse rates associated with tapering regimen
- Are the results likely to be biased in favour of tocilizumab because not all patients were in remission at the start of the trial (and the start of the tapering regimen)?
- Should the newly diagnosed and relapsing subgroups be considered separately?

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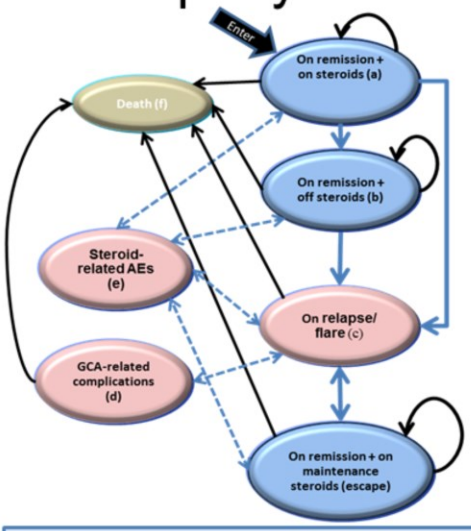
Company economic model structure



- 30 year time horizon
- 3.5% discount rate
- NHS/PSS perspective
- 7 day cycle length
- All patients enter in remission state
- Tocilizumab effectiveness captured by differences in time in remission, number of flares and GCA related complications as well as steroid-related adverse events

a. 26 weeks for tocilizumab+prednisone and 52 weeks for prednisone alone
b. Patients who have not yet flared after the end of tapering
c. Transition probabilities derived from K–M curves of time to first flare from GiACTA
d. Stroke and vision loss
e. Fractures and diabetes
f. Background mortality and GCA mortality taken into account

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Source: company submission figure 9

Key model drivers

Key drivers of incremental QALY gains for tocilizumab:

- Less time in flare state and longer time in remission state which has higher utility
- Less time taking steroids (as shorter taper) which is associated with disutility

Key drivers of cost differences:

- Additional acquisition costs of tocilizumab
- More flares in prednisolone group, each flare has a cost attached
- Weekly management costs on steroids higher than off steroids, tocilizumab group spends less time on steroids

QALYs				Costs*			
	Tociliz	Pred.	Increment		Tocilz	Pred.	Increment
Remission	8.66	7.80	0.86	Tociliz.	[redacted]	-	[redacted]
Flare	0.26	0.71	-0.45	Flare cost	[redacted]	[redacted]	[redacted]
GCA-related AEs	-0.01	-0.03	0.02	Disease man'mnt	[redacted]	[redacted]	[redacted]
Total	8.91	8.48	0.43	Total	[redacted]	[redacted]	[redacted]

*costs not included in table for: prednisolone, AEs and concomitant drugs: inc. difference <5%

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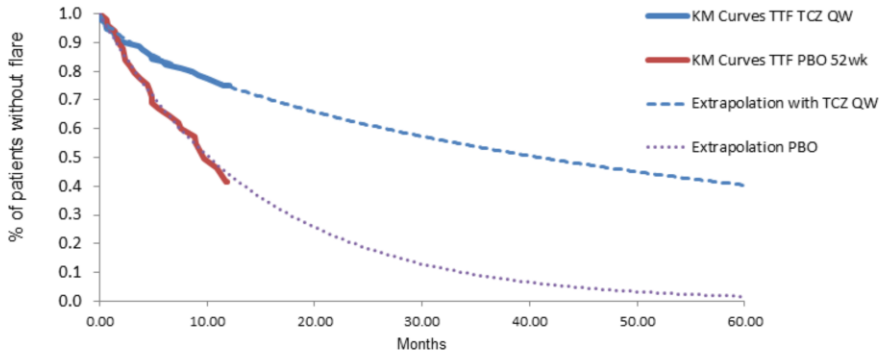
Source: ERG report tables 22 and 23

Transition: remission to relapse/first flare

- Transitions to relapse/first flare time dependent and estimated from time to first flare data from GiACTA, extrapolated beyond the trial time horizon
- Company chose distributions based on visual inspection and best statistical fit (lowest AIC) to overall population data and validated these using clinical opinion and market research
  - Weibull for tocilizumab and exponential for prednisolone (same distributions are used for newly diagnosed and relapsing subgroups)



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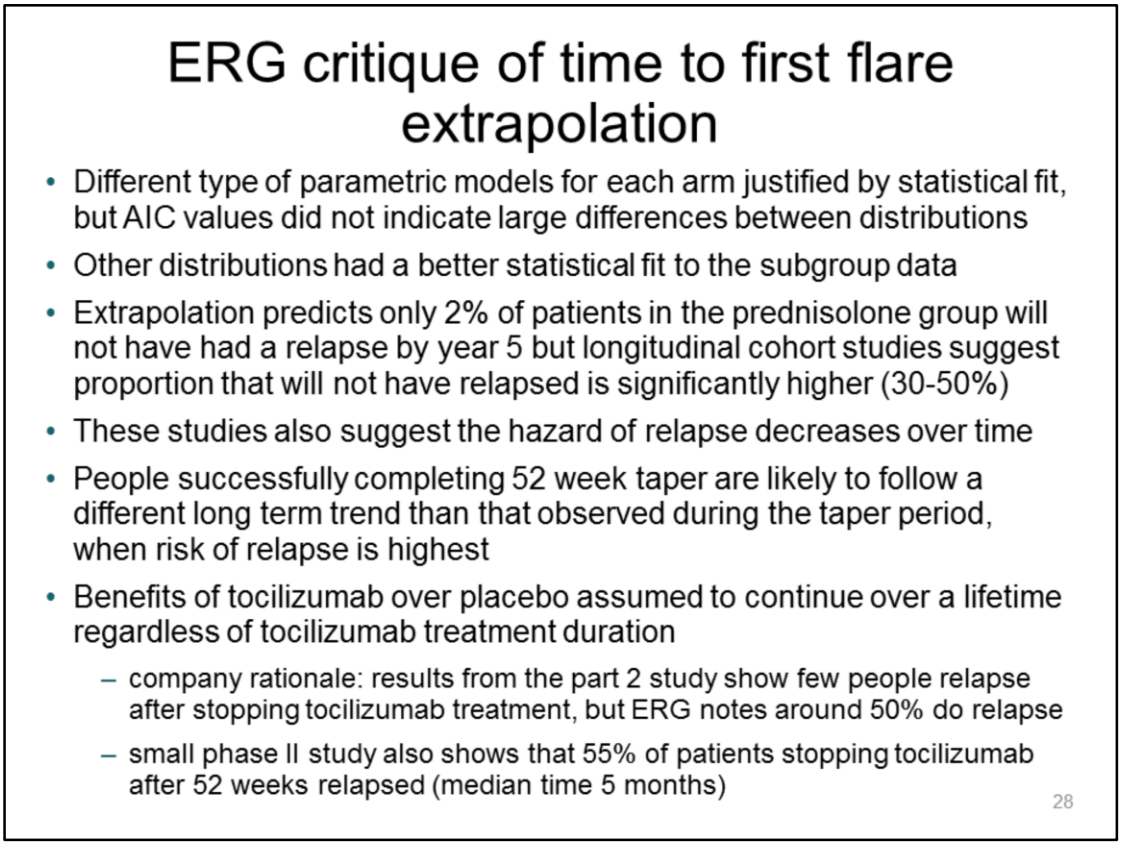
Source: company submission figure 11
For longer term extrapolation see ERG report figure 8



Longitudinal cohort studies:

- Alba et al. (2014) Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients
- Proven et al. (2003) Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes
- Labarca et al. (2016) Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study
- Restuccia et al. (2016) Flares in biopsy-proven giant cell arteritis in Northern Italy: characteristics and predictors in a long-term follow-up study

Transition: remission to subsequent flare

- Probability of subsequent flares estimated from GiACTA and assumed constant as flares can occur many years after diagnosis – company scenario analyses reduce probability by 5% and 10% per year

Weekly probability of flare	Overall population	Newly diagnosed	Relapsing
Tocilizumab	0.0106	0.0127	0.0083
Prednisolone	0.0228	0.0166	0.0285

ERG comment:

- Probabilities appear clinically logical for prednisolone – risk is higher for relapsing group than the newly diagnosed and overall populations, but this is not the case for tocilizumab group
- Total mean number of flares predicted by model over a 30 year period for the prednisolone overall population is 19.67 which lacks external validity
  - Proven (2003) reported a maximum of 7 flares in any single patient based on a median follow-up of 10 years - company model predicts mean of 10.35 over 10 years
  - Labarca (2015) reports median relapse rate of 0.4/year over 5 years i.e. ~2 relapses over 5 years - company model predicts 5.26 over 5 years

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Source: ERG report table 10

- ERG also note that the evidence informing the transitions is from a post-randomisation subset of the overall population and therefore not randomised and subject to potential confounding.
- Using the post-randomisation subset also introduces an important source of selection bias – the subset who experienced a flare during the GiACTA follow-up are unlikely to be representative of the overall population, as the prognosis of people who flare early in the course of treatment is likely to differ from that of those who flare later.
- ERG note that populations in the Proven and Labarca long-term follow-up studies may be more generalisable to the newly diagnosed subgroup, as they follow patients from diagnosis.

Adverse events

Giant cell arteritis related complications

- Can only be experienced by patients in the relapse/flare state
- Included complications are vision loss, major stroke and minor stroke
- Probabilities from literature as none of these events occurred in GiACTA

Steroid related adverse events

- Diabetes and fractures included in model
- Rates in GiACTA low, so risk calculated by extrapolating cumulative steroid doses and linking to Clinical Practice Research Datalink (CPRD)
- Predicted cumulative doses adjusted to match mean dose in CPRD data

ERG comment:

- Modelling of GCA complications assumes surrogate relationship between complications and flares and that risk is modifiable with tocilizumab
- CPRD dosing is more likely to reflect that for newly diagnosed group, higher doses may be more appropriate for relapsed group
- Adverse events have limited impact on ICER

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The CPRD is a database of NHS primary care records. As such, it captures primary care prescriptions but people with relapsing GCA may be more likely to be managed in secondary care and to receive higher cumulative doses of steroids

Utilities

- Utilities for remission and relapse calculated from EQ-5D in GiACTA
- Data was pooled across treatment arms as no significant differences
- Lower utility estimate for relapse/flare applied for 28 days

Health state utility values	Overall population	Newly diagnosed	Relapsed
Remission	0.771	0.812	0.733
Relapse/flare	0.642	0.645	0.634

- Disutility from taking steroids of -0.070 applied, reflecting range of common side-effects such as weight gain, appearance changes etc.
- GCA and steroid related adverse event disutilities derived from literature

GCA related AE disutility		Steroid related AE disutility	
Vision loss	-0.367	**Diabetes**	-0.093
Minor stroke	-0.179	**Fracture (year 1)**	-0.203
Major stroke	-0.491	**Fracture (year 2+)**	-0.113

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Source: ERG report tables 12 and 13
Reduction in utility due to flare is highest for newly diagnosed group (0.166) and lowest for relapsed group (0.099). Overall population: 0.129

Resources and costs

- Company revised analyses use prednisolone cost to reflect NHS practice
- No administration costs assumed for either tocilizumab or steroids
  - ERG concludes that administration of tocilizumab unlikely to generate significant cost implications not included in model
- Liver function monitoring costs for tocilizumab included in model

Weekly health state management costs

Remission + on steroids	Remission + off steroids	Remission + maintenance steroids	Cost per flare
£26.35	£4.32	£20.17	£259.77

- ERG note that the same weekly management costs were used for all groups but newly diagnosed have more frequent follow-up so higher costs for remission + on steroids state (£38.41)
- ERG corrects this and is presented alongside the company's scenario analyses later in this document

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Source: ERG report table 18

P84 ERG report:

- Company provide a homecare delivery and Health Check service for rheumatoid arthritis (RA) patients taking tocilizumab, which they plan to continue for GCA patients.
- Service includes up to 2 home visits by a qualified nurse to train the patient to self-administer subcutaneous tocilizumab.
- Currently a 90% uptake of homecare delivery for RA
- Health Check telephone service comprising up to 6 calls which includes advice and counselling on self-administration.

Company's deterministic base case *with PAS*

- **2 year treatment duration**

	Total flares	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Overall population						
Steroids	19.12	[redacted]	8.48	12,180	0.43	**£28,272**
Tocilizumab	6.52	[redacted]	8.91			
Newly diagnosed						
Steroids	14.48	[redacted]	9.02	13,302	0.35	**£37,334**
Tocilizumab	8.61	[redacted]	9.38			
Relapsing						
Steroids	25.59	[redacted]	8.24	10,993	0.49	**£22,403**
Tocilizumab	6.38	[redacted]	8.73			

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- Source company's clarification response
- ERG was unable to replicate the company's probabilistic ICER estimates and believe company made an error in implementing the PSA
- ERG's PSA estimate for overall population: £26,914, newly diagnosed: £35,766 and relapsing: £21,000 (see ERG report, tables 30-32. Note, figures in preceding text do not match those in table, due to different runs of the PSA)

Key company scenario analyses

ICERs (£/QALY)	Overall population	Newly diagnosed*	Relapsing*
Company base case	**£28,272**	**£37,334**	**£22,403**
Mean age: CPRD data (73 years) rather than GiACTA (69 years)	£33,195	£42,581	£28,093
1 year tocilizumab treatment rather than 2 years	£7,767	£12,354	£4,363
3 years tocilizumab treatment	£47,763	£61,080	£39,577
5% p.a reduction subsequent flare probability (instead of fixed rate)	£33,902	£41,524	£28,708
10% p.a reduction in flare probability	£37,977	£44,450	£33,395
Exponential distribution tocilizumab time to first flare (instead of Weibull)	£46,418	£71,693	£34,531
GiACTA mean steroid dose (14g) rather than 8.6g from CPRD	£25,695	£34,519	£20,260
ERG calculated weekly management costs	*£28,272*	*£35,797*	*£22,253*

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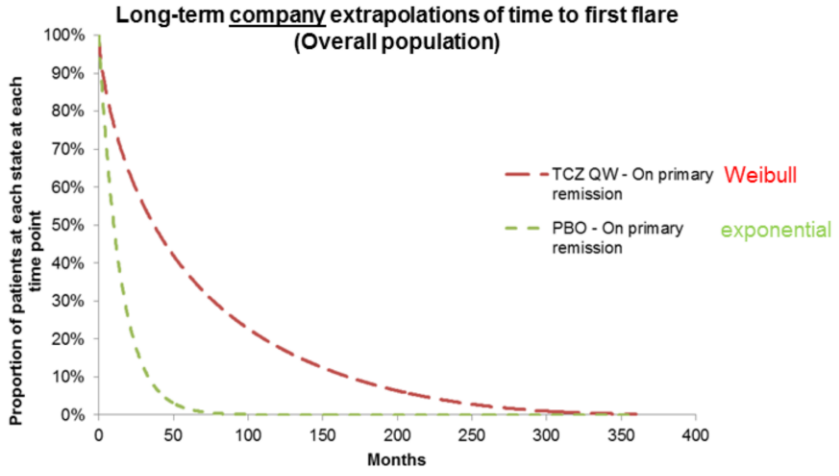
*ERG calculated

Scenarios for newly diagnosed and relapsing subgroups calculated by ERG
Source: company clarification response, ERG report tables 27, 28 and 29

Note: the scenario varying the tocilizumab treatment duration only affect the cost of tocilizumab. The treatment benefit is assumed to be the same regardless of length of treatment course (slides 36, 37 and 38 show that the incremental QALYs in this scenario are the same as when treatment duration is assumed to be 2 years, but the incremental costs are lower).

ERG alternative modelling: time to first flare

- Assumption that tocilizumab benefits continue over a lifetime regardless of treatment duration is not adequately justified
- This is partially implemented in model by use of treatment specific parametric distributions for the extrapolation period for time to first flare



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Source: ERG report figure 8

ERG alternative modelling: time to first flare

- More appropriate to use same distribution for tocilizumab and prednisolone:
  - long-term tocilizumab benefits uncertain, so inappropriate to assume benefit maintained after treatment stops
  - risk of flare highest during steroid taper; people successfully completing taper with and without tocilizumab may have common trajectory

Scenario 1a

- After tocilizumab treatment stops at 2 years, use exponential distribution for both treatments (as used by company for prednisolone alone extrapolation)
- However, a high number of flares is now predicted for tocilizumab as well as prednisolone (rather than just for prednisolone), at odds with the evidence from long-term follow-up studies

Scenario 1b

- After tocilizumab treatment stops at 2 years, use Weibull distribution for both treatments (as used by company for tocilizumab extrapolation)
- ERG prefer this scenario as:
  - Weibull assumes decreasing risk, reflecting long-term epidemiological data
  - Weibull fits tocilizumab data best and this arm may provide a better basis for projections of patients that have successfully tapered and not experienced a flare (more did so in this arm than in steroid only)

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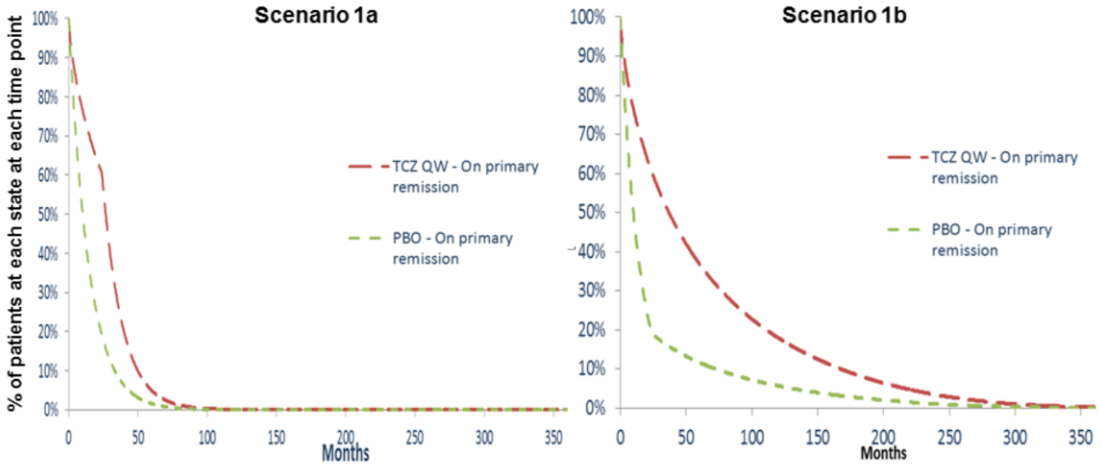
Note in scenario 1a) parametric curve based on Weibull is used for tocilizumab between 0 and 2 years and in scenario 1b) parametric curve based on exponential is used for prednisolone between 0 and 2 years

ERG alternative time to first flare extrapolation: Overall population



ERG prefers scenario 1b:

- Higher proportion on prednisolone in remission longer - 12% predicted to not have 1st flare by year 5 compared to <2% in company extrapolation/scenario 1a
  - more in line with longitudinal studies (30-50%)
- Lower number of flares predicted for both treatments over the model horizon

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Source: ERG figure 12

ERG alternative modelling: subsequent relapses

- Company probabilities of subsequent relapses inconsistent across tocilizumab subgroups and produce implausibly high estimates of flares
- Labarca study estimates 0.4 relapses/year (probability of 0.0076/week)
- ERG note that this rate may be most applicable to the newly diagnosed subgroup, as the study followed people from diagnosis
- ERG uses this rate for the prednisolone newly diagnosed subgroup, and derives rates for the other prednisolone subgroups and for the tocilizumab subgroups by estimating a series of hazard ratios
- This leads to logically consistent probabilities across subgroups
- These probabilities combined with time to 1st flare extrapolation scenario 1b produce lower, more plausible estimates of mean number of flares

Predicted mean number of flares over 30-year model horizon

	Overall population		Newly diagnosed		Relapsing	
	Company	ERG	Company	ERG	Company	ERG
Tocilizumab	6.5	4.0	8.6	3.1	6.4	4.9
Prednisolone	19.1	9.6	14.5	7.2	25.6	12.3

See ERG report table 40 for ERG's probabilities of subsequent flare

Source: ERG report tables 25, 26, 27 and 41, 42, 43

ERG scenarios and preferred base case
Overall population - *with PAS*

	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
2 year treatment duration			
Company base case	**12,180**	**0.43**	**28,272**
Mean age 73 (from CPRD data)	12,749	0.38	33,159
1b: prednisolone time to 1st flare, Weibull after year 2	12,156	0.37	32,661
2: revised probability of subsequent flare	13,371	0.34	39,579
ERG preferred [mean age 73 + scenario 1b + 2]	**14,110**	**0.21**	**65,801**
1 year treatment duration*			
Company	**3,346**	**0.43**	**7,767**
ERG	**5,296**	**0.14**	**36,960**

*results presented for 1 year due to uncertainty regarding appropriate duration of treatment. ERG believe 1 year is most internally valid as it is consistent with follow-up in GiACTA, but treatment may be longer in practice given ongoing relapse risk

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Source: company clarification response appendix tables 50, 54, 56
ERG report tables 37, 41, 44, 47

ERG scenarios and preferred base case
Newly diagnosed - *with PAS*

	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
2 year treatment duration			
Company base case	**13,302**	**0.35**	**37,334**
Mean age 73 (from CPRD data)	13,605	0.32	42,581
1b: prednisolone time to 1st flare, Weibull after year 2	12,604	0.28	44,338
2: revised probability of subsequent flare	13,440	0.33	41,322
ERG preferred [mean age 73 + scenario 1b + 2]	**13,748**	**0.19**	**73,046**
1 year treatment duration			
Company	**4,368**	**0.35**	**12,354**
ERG	**5,172**	**0.12**	**41,577**

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Source: company clarification response, table 25
ERG report: tables 27, 38, 42, 45, 48

Note: ERG preferred base case maintains the same weekly management costs for patients on remission + on steroids across all subgroups, as in company base case

ERG scenarios and preferred base case
Relapsing - *with PAS*

	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
2 year treatment duration			
Company base case	**10,993**	**0.49**	**22,403**
Mean age 73 (from CPRD data)	11,908	0.42	28,093
GiACTA mean steroid dose (14g) not CPRD (8.6g)*	9,942	0.49	20,260
1b: prednisolone time to 1st flare, Weibull after year 2	10,572	0.45	23,730
2: revised probability of subsequent flare	13,084	0.35	37,582
ERG preferred [mean age 73 + GiACTA steroid dose + scenario 1b + 2]	**12,967**	**0.22**	**58,411**
1 year treatment duration			
Company base case	**2,141**	**0.49**	**4,363**
ERG	**4,638**	**0.15**	**30,158**

*higher dose in GiACTA trial more likely to reflect the higher doses for this subgroup

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Source: company clarification response, table 29
ERG report: tables 28, 39, 43, 46, 49

Note: ERG preferred base case maintains the same weekly management costs for patients on remission + on steroids across all subgroups, as in company base case

Innovation and equality

- First new treatment option in this area for many years
- Steroids are associated with a high toxicity burden – high unmet need for treatments which are steroid-sparing
- Promising Innovative Medicine (PIM) designation for tocilizumab in GCA was issued by the MHRA in May 2017
- No additional benefits not captured in the QALY highlighted by company
- Age highlighted as a potential equality issue in submissions, as GCA predominantly affects people over 50 years
  - NICE will appraise tocilizumab for GCA in line with the marketing authorisation, which does not have restrictions by age. Any recommendations will not make it more difficult to access tocilizumab based on age compared with other groups

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Key cost effectiveness issues (1)

- How should time to first flare be extrapolated?
  - Company's extrapolation assumes constant benefit of tocilizumab over prednisolone regardless of duration of treatment
  - ERG suggests more appropriate to use same distribution after 2 years, either:
    - 1a) exponential as company used for prednisolone alone, but this predicts high number of relapses for both treatments
    - 1b) Weibull as company use for tocilizumab
  - ERG suggests Weibull is appropriate, as:
    - assumes declining risk over time, in line with epidemiological data
    - estimate of people not relapsed at 5 years more externally valid
    - fits tocilizumab arm best, which is based on more data than prednisolone

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Key cost effectiveness issues (2)

- How should rate of subsequent flare be modelled?
  - company estimates higher probability of subsequent flares for newly diagnosed population than relapsing population (tocilizumab arm) and high mean number of flares over model time horizon
  - ERG estimates logically consistent probabilities across subgroups and predicts a lower mean number of flares, in line with external data
- What is the most appropriate tocilizumab treatment duration?
  - company and ERG base cases assume 2 years, with scenarios assuming 1 year
  - 1 year is most internally valid estimate, consistent with treatment duration in GiACTA, but 2 years may be more externally valid
  - preliminary results of long term follow-up data suggests for sustained benefit, significant proportion of people need continued treatment
- What are the most plausible ICERs?
- Are there any additional benefits that have not been captured in the QALY calculation?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1051

Tocilizumab for treating Giant Cell Arteritis

Document B

Company evidence submission

August 2017

File name	Version	Contains confidential information	Date
ID1051 Roche submission for tocilizumab for GCA – main body [ACIC]	**1.0**	**Yes**	**10 August 2017**

Contents

Tables

Figures

Abbreviations

Acronym	Definition
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
AESI	Adverse events of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibodies
ARVO	Association for Research in Vision and Ophthalmology
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AWMSG	All Wales Medicines Strategy Group
BHPR	British Health Professionals in Rheumatology
BMC	BioMed Central
BMI	Body Mass Index
BNF	British National Formulary
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Conformité Européene
CEA	cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
CS	corticosteroid
CSR	clinical study report
CTLA	anti-cytotoxic T-lymphocyte antigen
CUA	cost utility analysis
CV	cardiovascular
DMARD	disease-modifying antirheumatic drugs
EE	economic evaluations

EPAR	European Public Assessment Report
EQ-5D	EuroQOL 5 Dimensions questionnaire
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	(US) Food and Drug Administration
FTP	Fast Track Pathway
FU	follow-up
GC	glucocorticoids
GCA	Giant Cell Arteritis
GP	General Practitioner
HCRU	Healthcare Resource Utilisation
HE&OR	Health Economics and Outcomes Research
HIRU	Health Information Research Unit
HR	hazard ratio
HRQL	health-related quality of fife
HSUV	health-state utility values
HTA	Health Technology Appraisal
HUI	health utility index
ICD-9-CM	International Classification of Diseases, Clinical Modification
ICER	incremental cost-effectiveness ratio
IL	Interleukin
IOVS	Investigative Ophthalmology & Visual Science
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISSG	Information Specialists' Sub-Group
ITT	intention-to-treat
IU	International Units
IV	intravenous
IVRS	Interactive Voice-Response System
KM	Kaplan-Meier
LTFU	long-term follow-up
LSM	least square means
LV	large vessel

LYG	life years gained
MCDA	multi criteria decision analysis
MCS	Mental Component Score
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
MR	magnetic resonance
MRU	Medical Resource Utilisation
MS	Microsoft
MTX	methotrexate
NA	not applicable
NE	not evaluable
NHS	National Health Service
NHS EED	NHS Evidence Evaluation Database
NICE	National Institute for Health and Care Excellence
NMSC	non-melanoma skin cancer
NR	not reported
NS	not significant
OCS	oral corticosteroids
OLE	open-label extension
PAS	patient access scheme
PBO	placebo
PCS	Physical Component Score
PGA	patient global assessment
PIM	Promising Innovative Medicine
PK	Pharmacokinetics
PMR	polymyalgia rheumatica
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRO	patient-reported outcomes
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PY	patient years
QALY	quality-adjusted life years
QW	once per week
RCT	randomised, controlled trial

SAE	serious adverse events
SAS	Statistical Analysis System
SC	subcutaneous
SD	standard deviation
SE	standard error
SF	Short Form
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SMQN	Standardised MedDRA Query, narrow (scope)
SOC	system organ class
STA	single technology appraisal
TAB	temporal artery biopsy
TB	tuberculosis
TCZ	tocilizumab
TNF	tumour necrosis factor
TTFF	time to first flare
UK	United Kingdom
ULN	upper limit of normal
US	ultra sound
VAS	visual analogue scale
VBA	Visual Basic for Applications
WHO	World Health Organisation

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full (anticipated) marketing authorisation for this indication:

The marketing authorisation relevant to this submission has not yet been published by the electronic Medicines Compendium (EMC); however, the Committee for Medicinal Products for Human Use (CHMP) Positive Opinion has been granted for tocilizumab for the treatment of Giant Cell Arteritis (GCA) in adult patients"

This submission matches the CHMP Positive Opinion population and the clinically relevant treatment of GCA patients.

Patients receive treatment for GCA in clinical practice when their disease becomes active; this is in line with the population included in the GiACTA pivotal trial which forms the basis of the CHMP positive opinion.

Tocilizumab is expected to be cost-effective within this patient population (base case ICER of £14,336 per QALY; see section B.3.7 Base-case results).

Table 1: The decision problem for appraising the cost-effectiveness of tocilizumab for treating people with GCA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with GCA	Adults with GCA	Paediatrics not included
Intervention	Tocilizumab	Tocilizumab	No difference
Comparator(s)	Established clinical management without tocilizumab	Established clinical management without tocilizumab (prednisone taper used within the GiACTA clinical trial; immunosuppressants permitted as concomitant medication)	GCs, such as prednisone, are the mainstay of treatment for people with GCA, both in newly diagnosed and in relapsed/refractory GCA. The British Society for Rheumatology guidelines also state that steroid-sparing agents can be combined with GCs to reduce the cumulative steroid burden, including immunosuppressants such as methotrexate (Dasgupta et al. 2010). However, published evidence for methotrexate in the treatment of GCA is inconsistent
Outcomes	The outcome measures to be considered include: • disease remission; • time to relapse after disease remission; • adverse effects of long term corticosteroid treatment (including weight gain, osteoporotic fractures and diabetes mellitus); • morbidity (including vision loss, stroke and aortic aneurysm) • mortality; • adverse effects of treatment; • health-related quality of life.	The following information is reported from the GiACTA trial: • disease remission; • time to relapse after disease remission; • GC exposure • adverse effects of treatment; • health-related quality of life. The main model inputs are: • time to first flare • time to subsequent flare • GC-related AEs (fractures, diabetes, osteoporosis, infections)	The information provided from the GiACTA trial matches the outcomes requested within the NICE scope and decision problem

		• GC-related complications (vision loss and stroke) • mortality • utility for the modelled health states	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As outlined in NICE's guide to the methods of technology appraisal, the cost-effectiveness case presented here will compare treatments according to the incremental cost per quality-adjusted life years gained. A 30 year time horizon is considered appropriate to capture the differences in costs and outcomes, which reflects a patient's lifetime, since GCA typically occurs in middle-aged and elderly people. Standard approaches to discounting will be included. As is typical, costs will be considered from an NHS and Personal Social Services perspective. The Patient Access Scheme for tocilizumab is included.	In line with the NICE scope
Subgroups to be considered	Subgroups stated include: • people with newly diagnosed GCA; • people with relapsed or refractory GCA	In addition to submitting the full ITT population analysis, clinical data has been submitted for two a priori defined patient subgroups: • people with newly diagnosed GCA, and • people with relapsed or refractory GCA	No difference
Special considerations including issues related to equity or equality		Tocilizumab was given Promising Innovative Medicine designation by the MHRA on 25 May 2017 for the treatment of GCA patients.	

B.1.2 Description of the technology being appraised

The table below describes tocilizumab in relation to this indication extension to include treatment for adults with GCA.

Table 2: Technology being appraised

UK approved name and brand name	Tocilizumab (RoActemra®)
Therapeutic class	Immunological agent
Mechanism of action	C-reactive protein and other acute phase reactants (APRs) that are increased by elevated circulating concentrations of interleukin-6 (IL-6) correlate with disease activity in GCA. Tocilizumab is a recombinant humanised IgG1 monoclonal antibody which targets soluble and membrane bound forms of the interleukin-6 receptor and inhibits IL-6 signalling in a competitive manner (Stone et al. 2017)
Marketing authorisation/CE mark status	CHMP Positive Opinion was granted on 20 July 2017 for subcutaneous tocilizumab in GCA; approval is anticipated in September 2017 The FDA approved tocilizumab subcutaneous injection for the treatment of GCA on 23 May 2017. (Genentech Inc 2016; Hoffmann-La Roche Ltd. 2017c)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Tocilizumab is indicated for the treatment of giant cell arteritis (GCA) in adult patients.
Method of administration and dosage	The recommended posology is subcutaneous tocilizumab 162 mg once every week in combination with a tapering course of glucocorticoids. Tocilizumab can be used alone following discontinuation of glucocorticoids. Tocilizumab monotherapy should not be used for the treatment of acute relapses. Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.
Additional tests or investigations	There are no additional tests needed prior to prescribing tocilizumab over and above that needed to diagnose GCA. Tocilizumab is subject to laboratory monitoring after start of treatment. (Hoffmann-La Roche Ltd. 2017a)
List price and average cost of a course of treatment	The marketing authorisation extension for RoActemra® for the treatment of people with GCA has initially been applied for with the subcutaneous formulation The list price for RoActemra® SC is: £913.12 for 4 pre-filled syringes with 162 mg tocilizumab A typical course of treatment of tocilizumab for a person with GCA could be a weekly, subcutaneous dose for 2 years (Warrington 2014), administered at home. A 2-year course of tocilizumab to treat GCA would then cost [redacted] (see section B.3.7 Base-case results)
Patient access scheme (if applicable)	A simple PAS discount has been agreed with the Department of Health for subcutaneous RoActemra®. The simple PAS is a discount of [redacted] off the list price. The PAS price for subcutaneous RoActemra® is: [redacted] for 4 pre-filled syringes with 162 mg tocilizumab A typical course of treatment of tocilizumab for a person with GCA could be a weekly, subcutaneous dose for 2 years, administered at home. A 2-year course of tocilizumab to treat GCA would cost [redacted] with PAS.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Giant Cell Arteritis (GCA) is a potentially life-threatening condition associated with substantial impairment of the day-to-day functioning of patients. It is a chronic systemic vasculitis affecting large and medium-sized arteries, encompassing cranial GCA, involving extracranial branches of the carotid arteries and large-vessel (LV) GCA, involving the aorta and its primary branches. (Weyand and Goronzy 2003)

Studies of mortality in GCA have shown conflicting results; Crow et al. showed that patients with GCA were more likely than age- and gender matched controls to die within the first five years following diagnosis but the results did not address whether GCA itself or consequences of treatment of GCA were directly responsible for this increase in mortality. (Crow et al. 2009)

Others have shown that, in a systematic review and meta-analysis, at a population level long term mortality is not increased in GCA; however, mortality risk may be increased in some patients, especially in a hospital setting, and may vary over time. (Hill et al. 2017) Yet other studies show that GCA is associated with slightly increased early and late mortality. (Baslund et al. 2015)

Cranial GCA is the most typical presentation, with a spectrum of clinical and laboratory abnormalities attributable to ischaemia and systemic inflammation. Common ischaemic complications include severe headache, scalp tenderness, and jaw claudication. The most feared complication of GCA is vision loss. Visual manifestations, ranging from transient diplopia and amaurosis fugax to sudden, unilateral or bilateral, partial or complete vision loss, are among the presenting symptoms or develop shortly after diagnosis in approximately 30% of patients. Even today, permanent vision loss affects approximately 15%–20% of patients. Once vision loss is established, it is almost always permanent, but it can be prevented by early intervention. (Borchers and Gershwin 2012) Other cranial manifestations include transient ischemic attacks and cerebrovascular accidents, occurring in 2%–4% of patients. (Salvarani et al. 2009); (Gonzalez-Gay et al. 2009)

Large-vessel GCA (LV GCA), which affects the aorta and its primary branches, particularly subclavian, axillary and proximal brachial arteries can lead to aortic aneurysms, aortic dissection (Warrington 2014) and coronary arteritis. (Butler, Mundy, and Shah 2010) The reported prevalence of large-vessel complications (aortic aneurysm and dissection and/or

large vessel stenosis ranges from 3% to 18%. (Nuenninghoff et al. 2003a; Gonzalez-Gay et al. 2005)

Both cranial and LV GCA are associated with frequent manifestations of systemic inflammation, e.g. polymyalgia rheumatic (PMR), fatigue, general malaise, fever, anorexia, weight loss, and night sweats, accompanied by elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in approximately 90% of patients. (Smetana and Shmerling 2002; Liozon et al. 2003; Gonzalez-Gay et al. 2005; Walvick and Walvick 2011)

B.1.3.2 Epidemiology

GCA is a relatively uncommon condition which primarily affects adults ≥50 years, the risk increasing with age. Highest rates are observed between 70 and 79 years. (Gonzalez-Gay et al. 2009; Petri et al. 2015) In women, GCA incidence peaks from age 70 to 79. In men, GCA incidence increases but plateaus, peaking at ≥80 years. In the Northern hemisphere there is a significant increase in incidence and prevalence with increasingly northerly latitudes. The highest incidence rates have been reported in Scandinavia and the UK at 20–30 cases per 100,000 people aged ≥50 years. (Gonzalez-Gay et al. 2009) (Watts RA 2014). The incidence of GCA in the UK is estimated at around 220 per million, in people aged over 40 years (NHS Choices) (Luqmani et al. 2016)

B.1.3.3 Current treatment

GCA represents a medical emergency, requiring prompt diagnosis and initiation of treatment to prevent sudden vision loss and other ischaemic complications. (Matteson et al. 2016) The cornerstone of GCA treatment is high dose glucocorticoids (GC) followed by long-term steroid tapering. (Mukhtyar et al. 2009; Dasgupta et al. 2010; Borchers and Gershwin 2012) Patients often experience steroid-related adverse events (AEs) due to the cumulative toxic burden of long-term, high-dose steroid treatment; GCA patients exposed to higher average daily GC doses are at significantly increased risk of developing diabetes, glaucoma, osteoporosis, fractures, serious infections, and death compared to those with lower doses (Wilson et al. 2017a, 2017g). In an elderly population with multiple pre-existing conditions this carries serious risks and may cause significant disability, impairing patients' quality of life (Jobard et al. 2017).

GCs (usually prednisone) are initiated at a dose of 40 to 60 mg/day if GCA is suspected or confirmed by biopsy or imaging. (Mukhtyar et al. 2009) Patients with complicated GCA, e.g. evolving vision loss or history of amaurosis fugax, are often treated with IV methylprednisolone (500 mg to 1 g) daily for 3 days. (Mazlumzadeh et al. 2006) Once signs and symptoms have subsided, typically after 2 to 4 weeks, GCs are gradually tapered (BSR

guidelines propose tapering over a minimum of 52 weeks).(Dasgupta et al. 2010) The decision to reduce GCs is based on regular assessment of clinical signs and symptoms and evaluation of ESR or CRP levels.

In the current treatment pathway with GCs, although the duration of glucocorticoid treatment varies by individual, in most cases GCs can be discontinued after 18 -24 months (Warrington 2014). For some, complete cessation of steroid treatment is impossible without the occurrence of relapse and at least 50% of GCA patients are reported to relapse during treatment reduction. (Petri et al. 2015; Wilson et al. 2017g) Relapse can occur at any stage during patients' disease. (Andersson, Malmvall, and Bengtsson 1986) The majority of relapses are associated with rapid tapering. (Dasgupta et al. 2010)

In some patients with cranial GCA, the disease can take a relapsing chronic course requiring indefinite low dose GC treatment. (Borchers and Gershwin 2012) Late vascular complications several years after a GCA diagnosis suggest that GC doses sufficient to abate the signs and symptoms of cranial GCA may be inadequate to suppress or prevent vascular lesions in the large arteries. (Nuenninghoff et al. 2003a; Borchers and Gershwin 2012)

Although GCs are highly effective at inducing remission in most GCA patients, they are associated with a high cumulative toxicity burden; 86% of patients experiencing GC-related AEs after 10 years of follow-up, including 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)

Treatment with high dose GCs, especially in an elderly population with multiple pre-existing comorbidities (e.g., diabetes, hypertension and osteoporosis) carries serious risks (Weyand and Goronzy 2014) and may cause significant disability, impairing patients' quality of life (QoL) (Jobard et al. 2017). Furthermore, clinical studies have shown that both GCA disease and its treatment are likely to profoundly impact patients' health-related quality of life; a quality of life study focussing on GCA demonstrated that in addition to their fear of vision loss, the factor that affected patients' quality of life most adversely was the need for recurrent, chronic courses of GCs. (Hellmann et al. 2003)

GC-related AEs are also known to impact quality of life for patients with GCA. Specifically, some evaluations of GCA assign a baseline disutility of 0.03 to all patients on GC therapy to reflect the disutility encountered as a result of common AEs, (e.g. weight gain, hirsutism, Cushingoid body habitus, skin changes). The disutility value also reflects the logistics of

treatment itself (e.g. frequent follow-up visits, trips to the pharmacy) that are experienced by most patients on GCs. (Niederkohr and Levin 2005; Luqmani et al. 2016)

A recent EULAR Taskforce (Strehl et al. 2016) has concluded that, although the risk of harm is low for a majority of patients with rheumatic diseases at long-term dosages of ≤5 mg GC equivalent per day, at dosages of >10 mg/day the risk of harm is elevated, which is expected to be increased with patient's age. Recently, Broder et al., 2017, interrogated a large Marketscan database with 2,497 GCA patients and found that for each 1000 mg increase in GC exposure, the hazard ratio increased by 3% for new GC-related adverse events and by 5% for new-onset diabetes mellitus.(Broder et al. 2016)

Given the seriousness of GC-related AEs, considerable efforts should be made to minimise the duration of treatment and the cumulative GC dose. (Dasgupta et al. 2010) Other immunosuppressive drugs have been considered as alternatives to GCs (or to reduce GCs), with limited success. No agents capable of maintaining disease remission once GC therapy has been discontinued have been approved. Consequently, optimal management of GCA patients by way of balancing disease control and avoiding GCA-related complications whilst minimising GC-toxicity remains a complex challenge for treating physicians.

B.1.3.4 Other Immunosuppressants for GCA

Some guidelines recommend methotrexate (MTX)[1] as adjunctive therapy (Warrington and Matteson 2007) (Mukhtyar et al. 2009; Dasgupta et al. 2010) However, available evidence for methotrexate in GCA is limited and trials have yielded equivocal results (Jover et al. 2001; Spiera et al. 2001; Hoffman et al. 2002). A meta-analysis of individual patient data from trials demonstrated a modest reduction in relapse and GC exposure in the methotrexate treated groups. (Mahr et al. 2007) However, a further meta-analysis of the same trials concluded there was no significant benefit. (Yates et al. 2014)

Open-label studies have explored the effects of cyclosporine A, leflunomide, mycophenolate mofetil or cyclophosphamide in GCA but patient numbers were too small to draw conclusions about efficacy (Schaufelberger, Andersson, and Nordborg 1998; Quartuccio et al. 2012) (Adizie et al. 2012; Sciascia et al. 2012). Randomised clinical trials of anti-TNFα agents, including infliximab, adalimumab, and etanercept, have shown no efficacy in GCA. (Hoffman et al. 2007; Martinez-Taboada et al. 2008; Seror et al. 2014)

A recent Phase II trial of the CTLA-4 inhibitor abatacept has shown some evidence of efficacy in 49 patients. (Langford et al. 2017) However, data require further substantiation.

[1] Regular monthly blood monitoring is required for patients taking MTX

B.1.3.5 Prognosis

The general failure of GCs to induce long-term remission after dose tapering or discontinuation is driving the requirement for long-term GC treatment courses that are associated with toxicity.

Overall, the life expectancy of patients with GCA is similar to that of the general population. However, a late complication from GCA that influences survival is development of aortic aneurysms. Patients with GCA have a 17-fold increased risk for thoracic aneurysm and a 2.4-fold increased risk for abdominal aneurysm. (Evans, O'Fallon, and Hunder 1995) Aortic aneurysm may lead to aortic dissection, which can lead to a marked increase in risk of mortality (median survival 1.6 years after GCA diagnosis compared to 10.9 years in patients without LV complications). (Nuenninghoff et al. 2003c)

GCA is also associated with mortality due to other manifestations of LV and cranial arteritis such as fatal myocardial infarction, fatal stroke, and thromboembolic events (Crow et al. 2009; Luqmani et al. 2016).

Ophthalmic complications are common and include blurred vision, diplopia, amaurosis fugax, arteritic anterior ischemic optic neuropathy and blindness due to involvement of the ophthalmic artery. Vision loss can be sudden, temporary or permanent, partial or complete and can occur in one eye or both eyes. Vision damage that occurs before initiation of therapy is often irreversible (Foroozan et al. 2003); however, rates of vision loss are far lower after diagnosis, so long as treatment escalation can be provided rapidly upon relapse/flare. (Luqmani et al. 2016)

A large proportion of GCA patients will experience relapses/flares which often occur in the context of glucocorticoid therapy, and in some cases, adjunctive immunosuppressive therapy. Relapse can occur at any stage during patients' disease. (Andersson, Malmvall, and Bengtsson 1986) The majority of relapses are associated with rapid tapering. (Dasgupta et al. 2010) Headache, fatigue, muscle weakness and PMR are commonly reported symptoms during relapse/flare. Since a relapse/flare requires an increase in GC dose, these patients experience longer periods of treatment and are exposed to higher cumulative GC doses and therefore more GC-related AEs. Studies have reported GC-related AEs in 90%-95% of GCA patients within the first 3 years of therapy, including new or worsening hypertension (22%–84%), infections (22%–56%), osteoporosis and bone fractures (8%-38%), new or worsening diabetes mellitus (7%–37%) and cataracts (4%–41%). (Alba et al. 2014; Luqmani et al. 2016) There remains therefore a need for therapeutic agents that are

better able to induce and sustain long-term remission in patients with GCA both to avoid GCA-related complications and GC-related AEs. (Kermani et al. 2013).

The variability in the reported prevalence of relapses/flares (~43% of patients in population-based studies and up to 80% in clinical trials with adjuvant therapies), may be related to heterogeneity in the definition of relapses and to variability in the GC-tapering schedules. Alternatively, it could be recognised that people within a clinical trial will be more closely monitored for deterioration in their health. The definition of relapse, flare, or recurrence considerably varies across different studies. While in some publications definition of relapse has been based on clinical grounds, in others, isolated increases in acute-phase reactants have been considered disease flares. (Alba et al. 2014)

B.1.3.6 Clinical pathway of care

GCA is a rheumatic disease subject to wide variations of clinical practice and multiple referral routes in the UK both at diagnosis and at relapse/flare. The variation in referral routes arises since diagnosis is often difficult (symptoms are similar to many common conditions routinely seen by GPs and healthcare professionals) and it is often managed in primary care by general practitioners or in secondary care by rheumatologists, non-rheumatologists and ophthalmologists. (Dasgupta et al. 2010) Additionally, as symptoms of GCA are often acute and can constitute a medical emergency, patients may present in A&E (either directly, or by referral). (Research Partnerships 2017) This can also lead to differences and discrepancies in approach to both the perception of the disease, its severity, relapse/flare rates and treatment. In addition a “Fast Track Pathway” (FTP) has also been introduced in some centres across the UK from 2012, to secure early referrals, reduce multiple referral routes, standardise assessment and ensure rapid review and treatment of patients with suspected disease to improve patient outcomes (Patil et al. 2015).

There is currently no NICE guideline for GCA. However, the British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR) and European League Against Rheumatism (EULAR), have developed clinical practice guidelines to support the diagnosis and management of GCA and large vessel vasculitis. (Mukhtyar et al. 2009; Dasgupta et al. 2010)

An update to the BSR Guidelines on diagnosis and treatment of GCA is currently in development.

Table 3: International and national guidelines for diagnosis and management of GCA

Society	Year	Focus of guidelines
European League Against Rheumatism (EULAR) (Mukhtyar et al. 2009)	2009	Large vessel vasculitis including GCA
British Society for Rheumatology / British Health Professionals in Rheumatology (BHPR) (Dasgupta et al. 2010)	2010	Diagnosis and management of GCA

The key recommendations from the BSR guidelines 2010 include:

- Early recognition and diagnosis of GCA
- Urgent referral for specialist evaluation; a temporal artery biopsy (TAB) should be considered whenever a diagnosis of GCA is suspected. This should not delay the prompt institution of high-dose glucocorticoid therapy
- Immediate initiation of high-dose glucocorticoid treatment after clinical suspicion of GCA is raised
- Glucocorticoid reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease
- Recommended frequency of follow-up
    - Weeks 0, 1, 3, 6 and then Months 3, 6, 9, 12 in the first year
    - Extra unscheduled visits may be necessary in the event of relapse or adverse events
    - Later (Month 3 onwards) follow-up can be undertaken under shared care.

Recommendations specifically on GC initiation are:

Table 4: BSR/BHPR guidelines

Condition	Glucocorticoid dose
Uncomplicated GCA	
No jaw or tongue claudication or visual symptoms	Prednisolone 40-60 mg (not <0.75 mg/kg) daily until resolution of symptoms and laboratory abnormalities
Complicated GCA	
Evolving visual loss or history of amaurosis fugax	IV methylprednisolone 500 mg-1 g daily for 3 days
Established vision loss	≥60 mg prednisolone daily

(Dasgupta et al. 2010)

The BSR and BHPR guideline also gives a suggested GC tapering regimen:

- 40–60 mg prednisolone (not <0.75 mg/kg) daily continued for 4 weeks (until resolution of symptoms and laboratory abnormalities)

- Then dose is reduced by 10 mg every 2 weeks to 20 mg
- Then by 2.5 mg every 2–4 weeks to 10 mg
- Then by 1 mg every 1–2 months provided there is no relapse

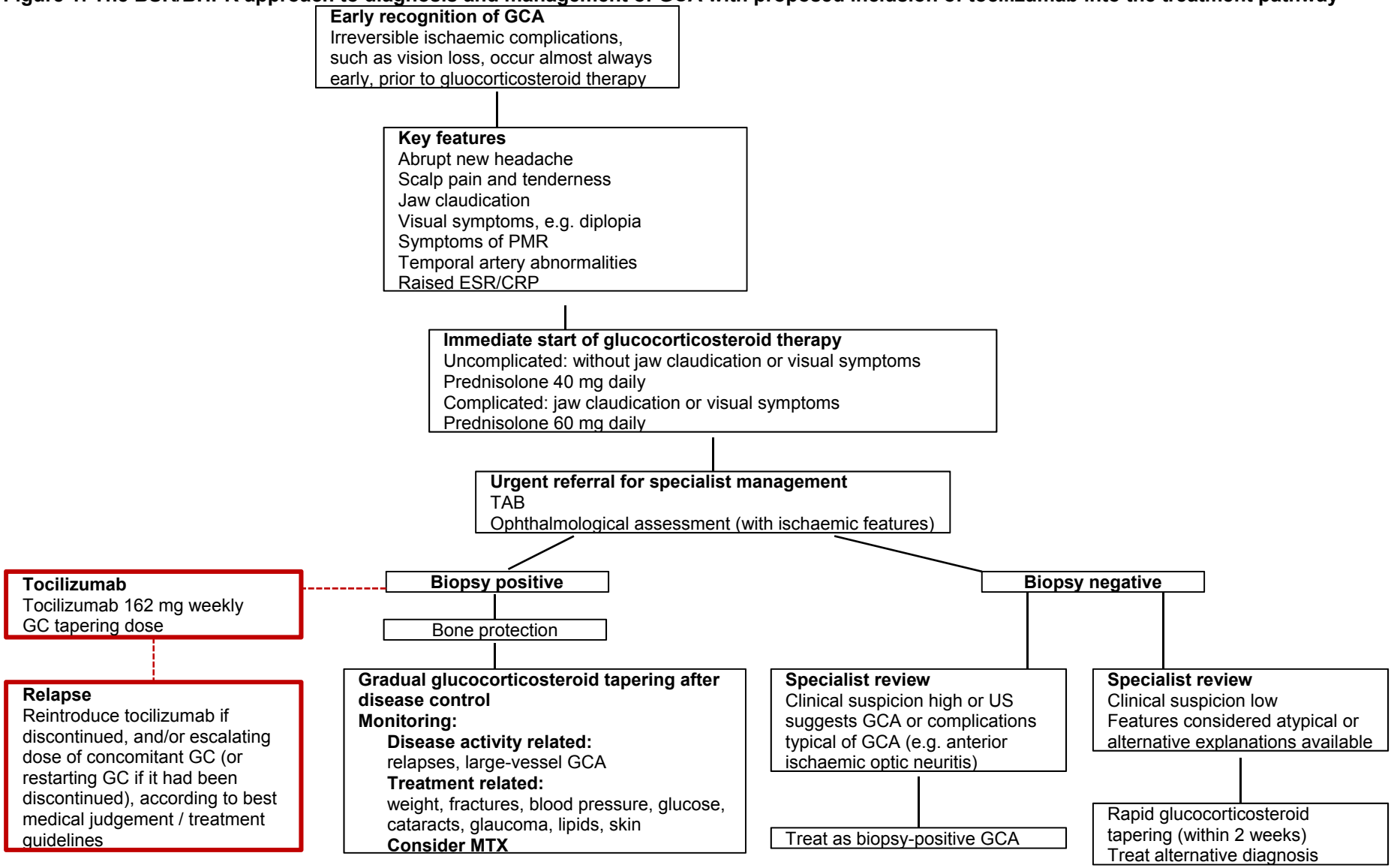
The tapering regimen adds up to a minimum of 52 weeks. This would give patients a cumulative GC burden of between 3.6 g and 7.4 g over approximately 1–1.5 years, in those patients who do not experience a relapse/flare. If patients flare, guidelines recommend increasing the GC dose and then tapering, with a subsequent considerable increase in the cumulative GC dose and an increased risk of GC-related AEs due to prolonged use of these drugs.

When patients relapse/flare, the BSR guidelines recommend different approaches depending on symptoms and severity:

- Headache: treat with the previous higher glucocorticoid dosage
- Headache and jaw claudication: treat with 60 mg prednisolone
- Eye symptoms: treat with either 60 mg prednisolone or intravenous (i.v.) methylprednisolone
- Large-vessel GCA (prominent systemic symptoms, limb claudication, persistent high-inflammatory markers): investigate with imaging techniques and consider treatment using systemic vasculitis protocols
- Introduction of MTX or alternative immunosuppressants should be considered as adjuvant therapy

The BSR/BHPR guidelines recommend an approach to diagnosis and management of GCA as summarised in Figure 1.(Dasgupta et al. 2010) Roche's suggestion of where tocilizumab would fit in this pathway is shown in red (note that these guidelines were written prior to a licence being granted for tocilizumab in GCA).

Figure 1: The BSR/BHPR approach to diagnosis and management of GCA with proposed inclusion of tocilizumab into the treatment pathway



(Dasgupta et al. 2010)

B.1.3.7 External expert input

Expert advisory panel

An expert advisory board was convened to provide feedback on the assumptions used to develop the health economic model and to optimise the model, to discuss clinical and economic data evaluation (including identifying gaps) on the clinical plausibility of results, appraisal comparators, model structure, resource use, and utility inputs.

Ten experts were approached, and seven attended. The panel was selected based on their familiarity with the treatment pathway relevant for GCA patients.

The panel consisted of consultant rheumatologists and ophthalmologists specialising in the management of patients with GCA. In addition, the panel included one independent expert health economist.

At the one day meeting, invited experts were briefed on the economic model structure and sources of key data inputs. Several facilitated group discussions were held; advisors' comments were recorded and taken into account in the subsequent development of the model.

Topics for discussion included:

- frequency of relapse/flare (including different populations), and implications for health economic model
- treatment for flare, including routes to accessing treatment and specialist consultants involved in treating relapse/flare
- complications of uncontrolled GCA
- current GCA treatments

Ad-hoc clinical expert validation

We have consulted on an ad-hoc basis with two rheumatologists with special interest in GCA and independent expert health economics consultants, to validate both clinical and economic assumptions.

B.1.4 Equality considerations

No equality issues relating to tocilizumab have been identified.

B.2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised. The systematic literature review and subsequent selection according to the scope of this submission revealed two studies, both investigating tocilizumab.

B.2.2 List of relevant clinical effectiveness evidence

Tocilizumab (TCZ) has been co-developed by F. Hoffman-la Roche Ltd. and Chugai Pharmaceutical Co. Ltd.

The efficacy and safety of tocilizumab in GCA has been demonstrated in several case series[2](Seitz et al. 2011; Unizony et al. 2012; Oliveira et al. 2014; Loricera et al. 2015) which led to the initiation of one small Phase II (Villiger et al. 2016) and one large Phase III clinical trial(Hoffman-La Roche Ltd. 2016) in patients with GCA. These studies formed the basis of the regulatory submissions, including long-term follow-up data, where available. The landmark international Phase III study, conducted by Roche, is the largest clinical study conducted in GCA.

- Phase III GiACTA trial [NCT01791153] (also known internally by Roche as WA28119)
- Phase II trial [NCT01450137] (known internally by Roche as ML25676)

Results from GiACTA were presented at the American College of Rheumatology (ACR) Annual Scientific Meeting in November 2016 (Stone et al. 2016) and a manuscript detailing the clinical methods has been published. (Tuckwell et al. 2016) The results have been published in a manuscript in July 2017. (Stone et al. 2017) Full data from the 2-year follow-up of patients enrolled in the Phase III GiACTA study will not be available until mid-2018; however, data on 88 patients who had completed at least 100 weeks of follow-up was included in the Regulatory dossier and is also summarised here for completeness. The clinical effectiveness evidence available from these trials is summarised below in Table 5.

Subsequent to the systematic literature review (SLR) being performed, the GiACTA study was published on 27th July 2017 in NEJM (*Trial of Tocilizumab in Giant-Cell Arteritis*, N Engl J Med 2017; 377:317-328, Stone et al.). (Stone et al. 2017) The peer-reviewed publication

[2] Not reported here as they are not RCTs

has been quoted in the submission (data from the clinical study report [CSR] has also been presented in this submission).

Efficacy data from study investigator-initiated Phase II NCT01450137 trial (Villiger et al. 2016) was not incorporated into the cost-effectiveness modelling but are included in Appendix K (methodology, results, etc.). The results of this study support the evaluation of the efficacy and safety of TCZ + GC treatment compared to GC treatment alone in the induction and maintenance of disease remission in patients with new-onset and relapsing GCA. Follow-up data are available in abstract form (Adler S 2016) and describe longer-term outcomes beyond week 52 at which point TCZ medication was stopped. In the follow up, patients were followed for a median time of an additional 12.5 months. (Adler S 2016) This study was not included in the economic model because there were notable differences in treatment regimens and study design (making the two studies non-comparable), namely:

- In GiACTA, patients received TCZ at a dose of 162 mg subcutaneously (SC) every 1 or 2 weeks, whereas in Phase II NCT01450137 trial, patients received TCZ at a dose of 8 mg/kg intravenously (IV) every 4 weeks
- in GiACTA, the primary endpoint was evaluated at Week 52, whereas in Phase II NCT01450137 trial the primary endpoint was evaluated at Week 12
- In GiACTA patients were receiving 0 mg/day GC at the time of the primary analysis, whereas in Phase II NCT01450137 trial the GC dose was 0.1 mg/kg/day at the time of the primary analysis
- The GC taper was standardised and blinded in GiACTA but not in Phase II NCT01450137
- In GiACTA, ESR and CRP were blinded and a Dual Assessor Approach was implemented to manage evaluation of ESR by the GCA assessor, whereas acute phase reactants were not blinded in the Phase II NCT01450137 trial

Table 5: Clinical effectiveness evidence

Study	Phase II NCT01450137 Trial					Phase III GiACTA Trial				
Study design	A Swiss single centre, Phase II, randomised, placebo-controlled study					A multicentre, randomised, double-blind, placebo-controlled study				
Population	Newly diagnosed or recurrent GCA					Newly diagnosed and relapsing GCA				
Intervention(s)	Tocilizumab (IV) + GC taper					Tocilizumab (SC) + GC taper				
Comparator(s)	Placebo (IV) + GC taper					Placebo (SC) + GC taper				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes		Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	✓	No			No	
Rationale for use/non-use in the model	Data from this trial are not included in the cost-effectiveness modelling. This Phase II trial used the IV formulation of tocilizumab. The primary endpoint was defined as complete remission at week 12 at a GC dose of 0.1mg/kg These parameters were not comparable to GiACTA and data were therefore not included in the model					This is the pivotal trial evaluating the efficacy and safety of tocilizumab in treating GCA. The evidence from this trial forms the randomised, controlled trial evidence included in the cost-effectiveness modelling.				
Reported outcomes specified in the decision problem	Proportion of patients who achieved complete remission of disease at week 12					**Sustained remission and adherence to GC taper regimen at week 52** **Time to GCA disease flare after clinical remission** **Adverse effects** **Morbidity (including vision loss, stroke)** **Mortality** **Health-related quality of life:** **Patient reported outcomes (PROs)** were assessed through four separate generic instruments: , EQ 5D; a visual analogue scale (VAS) patient global assessment (PGA); SF-36;and functional assessment of chronic illness therapy-fatigue (FACIT)				
All other reported outcomes						**Proportion of patients in sustained remission from weeks 12 to 52 and adherence to the GC taper compared with a 52-week (long course) GC taper given alone in a second placebo group.** **Cumulative GC dose**				

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the methodology of the Phase III GiACTA trial is shown in Table 6. (Note that a summary of the methodology of the Phase II NCT01450137 trial is given in Appendix K.)

Table 6: Summary of Phase III GiACTA trial methodology

Trial name	Phase III GiACTA
Location	UK, Austria, Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden, US
Trial design	A Phase III, multicentre, randomised, double-blind, placebo-controlled study
Eligibility criteria for participants	Key inclusion criteria: Aged ≥50 years New-onset GCA (diagnosed <6 weeks before baseline visit) or relapsing GCA (diagnosed >6 weeks before baseline visit and previous treatment with ≥40 mg/day GC [or equivalent] for ≥2 consecutive weeks at any time) Active disease within 6 weeks of baseline visit Key exclusion criteria: Major ischemic event, unrelated to GCA, within 12 weeks of screening Treatment with any investigational agent within 12 weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening Previous treatment with cell-depleting therapies, including investigational agents Previous treatment with TCZ Patients requiring systemic glucocorticoids for conditions other than GCA, which, in the opinion of the investigator, would interfere with adherence to the fixed glucocorticoid taper regimen and/or to assessment of efficacy in response to the test article Chronic use of systemic glucocorticoids for > 4 years or inability, in the opinion of the investigator, to withdraw glucocorticoid treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency Receipt of >100 mg daily intravenous methylprednisolone within 6 weeks of baseline
Trial drugs	Intervention: tocilizumab (1 mL, ready-to-use, single-use pre-filled syringe, each delivering 162 mg TCZ in 0.9 mL. All treatment groups followed either a short or long GC taper regimen according to a defined schedule. Prednisone/placebo tablets/capsules were taken daily for 52 weeks regardless of taper assignment Comparator: Placebo

Permitted concomitant medication	Aspirin or clopidogrel according to local practice and at the discretion of the investigator Oral calcium and 25-hydroxy vitamin D supplementation unless contraindicated (calcium 1200-1500 mg and vitamin D 800–1000 IU daily in divided doses) Bisphosphonate therapy (e.g. alendronate 70 mg weekly or zoledronate 4 mg annually) unless contraindicated administered at the discretion of the investigator Lipid lowering agents in patients with elevated lipids in conjunction with the investigator's clinical judgment and guidelines Short-term glucocorticoids could be administered in addition to the protocol-defined GC taper regimen Methotrexate: the dose was to remain stable and not be increased through screening and during the double-blind period. During the study the MTX dose could be reduced or discontinued if necessary for safety reasons
Disallowed concomitant medication	Previous treatment with cell-depleting therapies, including investigational agents Previous treatment with tocilizumab Immunisation with a live/attenuated vaccine within ≤4 weeks prior to baseline Receipt of >100 mg daily intravenous methylprednisolone within 6 weeks of baseline*
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy objective for this study was: Proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined GC taper regimen. Induction of remission had to occur within 12 weeks of randomisation Remission was defined as the absence of flare (as defined above) and normalization of C-reactive protein (CRP < 1 mg/dL) Sustained remission was defined as absence of flare following induction of remission up to the 52-week timepoint Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/h attributable to GCA
Other outcomes used in the economic model/specified in the scope	Secondary endpoints • Time to GCA flare after disease remission Safety endpoints PRO endpoints • Health-related quality of life
Pre-planned subgroups	New-onset patients Relapsing patients Starting GC dose (≤30 mg/day, >30 mg/day)

	Previous history of remission Imaging or biopsy at diagnosis GCA diagnosis based on 1990 ACR criteria for the classification of GCA GCA signs and symptoms at the time of diagnosis
Safety reporting and analyses	Analysis of safety data was based on the safety population. The safety population included all patients who received at least one administration of study drug and provided at least one post-dose safety assessment (withdrawal, adverse event [AE], death, laboratory assessment, or vital sign assessment). Patients were summarized according to the treatment they actually received

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
* Full list of exclusions related to concomitant therapy available in CSR
ACR: American College of Rheumatology; GCA: giant cell arteritis

B.2.3.1 Phase III GiACTA trial design

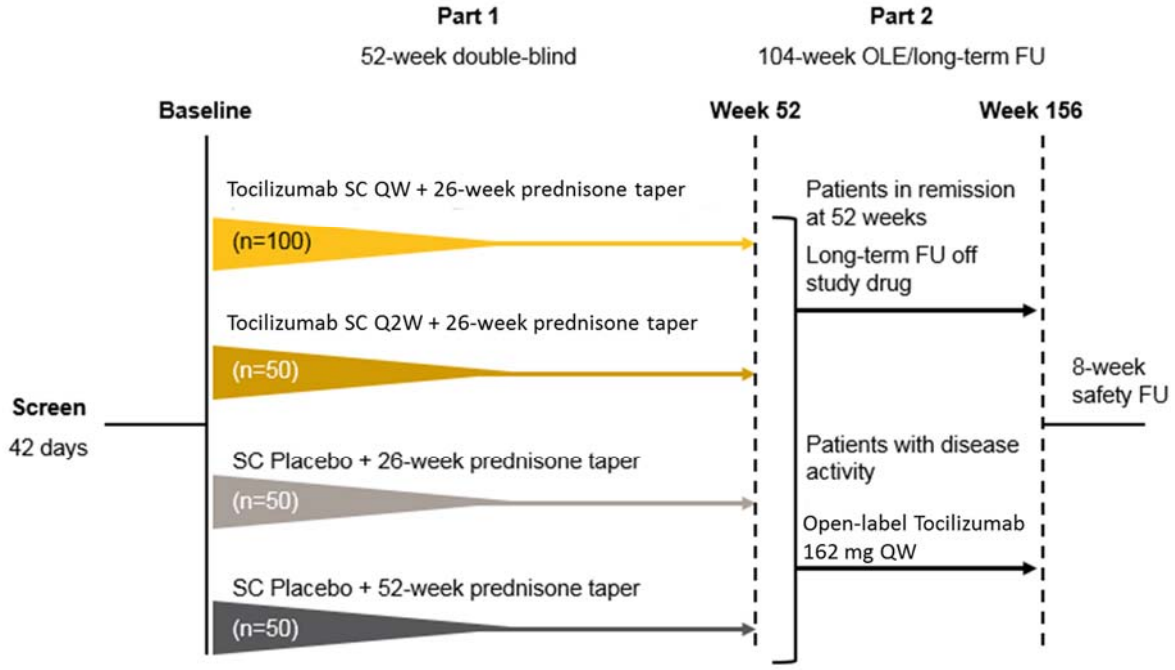
Patients older than 50 years of age with new onset or relapsing GCA were included in the GiACTA trial. A total of 251 patients were enrolled into the study and randomised to one of four study arms (Tuckwell et al. 2016); in a 2:1:1:1 ratio:

- QW SC tocilizumab 162 mg + 26-week GC taper (TCZ-QW);
- Q2W SC tocilizumab 162 mg + 26-week GC taper (TCZ-Q2W);
- QW SC placebo + 26-week GC (PBO+26-week GC);
- QW SC placebo + 52-week GC taper+ (PBO+52-week GC).

Randomisation was stratified by baseline GC dose (≤30 or >30 mg per day). An initial GC dose between 20 and 60 mg per day was selected by the investigator based on clinical judgment of the dose required to control the patient's GCA. Prednisone was then administered open-label at doses ≥20 mg per day and tapered according to weekly, protocol-defined decrements. Doses <20 mg per day were blinded. Patients who experienced flare, received escape therapy, withdrew from the trial, did not adhere to the protocol-defined GC taper, or did not achieve remission by Week 12 were considered non-responders. (Stone et al. 2017)

Part 1 of GiACTA completed in April 2016. (Figure 2)

Figure 2: Phase III GiACTA study design (Tuckwell et al. 2016)



FU: follow up; OLE: open-label extension; QW: every week; Q2W: every 2 weeks; SC: subcutaneous tocilizumab dose 162mg SC either QW or Q2W until Week 52

Part 2: Open-label extension / Long-term follow-up

Part 2 is an open-label extension which includes patients who have completed Part 1 and who will be followed for an additional 2 years. Note that the OLE/LTFU is on-going. A complete dataset is not yet available for Part 2. Results have not be presented or published, and do not appear in the Clinical Study Report. Initial data were included in the Regulatory Dossier submitted to the EMA. Since this data is discussed in later sections of this submission, we include the design of Part 2 here for completeness. (Design of Part 2 is presented in the Study Protocol as part of the Clinical Study Report.)

After the 52-week double-blind treatment period, all patients will enter Part 2 (open-label extension/long-term follow-up) of the study; see Figure 2. The purpose of the open-label extension/long-term follow-up is to describe the long-term safety and maintenance of efficacy after 52 weeks of therapy with tocilizumab in GCA, to explore a potential requirement for tocilizumab therapy beyond 52 weeks, and to gain insight into the potential long-term GC-sparing effect of tocilizumab.(Hoffman-La Roche Ltd. 2016)

Use of open-label tocilizumab at the Week 52 visit was dependent on the remission status of the patient at that visit:

- If a patient is in remission at Week 52, (either due to being in sustained remission from Week 12 to Week 52 or due to being in remission induced by escape GC) the treatment with double-blind injections of tocilizumab/placebo will be stopped. The patient will continue to be followed up in Part 2 of the study for maintenance of remission. (Hoffman-La Roche Ltd. 2016)

- If a patient is not in remission at the Week 52 visit or if a patient relapses/flares at any time during Part 2, they may be treated with open-label tocilizumab 162 mg QW at the discretion of the investigator.(Hoffman-La Roche Ltd. 2016)

A patient's GCA therapy can be adjusted at any time during Part 2 of the study at the investigator's discretion and on the basis of disease activity. This can include initiation/termination of open-label tocilizumab 162 mg QW and/or changes to GC or MTX treatment. (Hoffman-La Roche Ltd. 2016)

At the end of Part 2 of the study (Week 156), the study will end. (Hoffman-La Roche Ltd. 2016)

B.2.3.2 Baseline characteristics

A summary of the baseline characteristics of the Phase III GiACTA trial is shown in Table 7. (Note that a summary of the baseline characteristics of the Phase II NCT01450137 trial is given in Appendix K.)

The mean age of randomised patients was 69 years (SD: ±8.2 years), most patients were female (74.9%) and almost all patients were white (96.8%) (Tuckwell et al. 2016). The patients enrolled in GiACTA closely represent the real-world GCA population according to evidence from the US MarketScan database and the UK Clinical Practice Research Datalink (CPRD), which show similar patient demographics (mean age 71 years and 71% female) (Petri et al. 2015; Broder et al. 2016).

In the GiACTA study, 47% of patients in GiACTA had newly-diagnosed GCA and 53% had relapsing GCA (Tuckwell et al. 2016).

Table 7: Baseline demographics and disease characteristics for Phase III GiACTA trial (All-patient population)

	TCZ-QW n=100	TCZ-Q2W n=50	PBO+26-week GC taper n=50	PBO +52-week GC taper n=51
Age, years, mean (SD)	69.5 (8.5)	69.4 (8.2)	69.3 (8.1)	67.8 (7.7)
Females, n (%)	78 (78.0)	35 (70.0)	38 (76.0)	37 (72.5)
Race/Ethnicity, n (%)				
Asian	0	1 (2.0)	0	0
Black or African American	1 (1.0)	0	0	2 (3.9)
Other	1 (1.0)	1 (2.0)	0	0
White	97 (97.0)	47 (94.0)	50 (100.0)	49 (96.1)
Unknown	1 (1.0)	1 (2.0)	0	0
Weight, kg, mean (SD)	69.8 (13.8)	70.8 (16.1)	70.1 (15.8)	73.1 (15.3)
BMI	26.0 (4.4)	26.0 (6.2)	25.7 (4.5)	25.8 (4.1)
Newly diagnosed GCA, n (%)	47 (47.0)	26 (52.0)	23 (46.0)	23 (45.1)
Relapsing GCA, n (%)	53 (53.0)	24 (48.0)	27 (54.0)	28 (54.9)
Prednisone dose, n (%)				
≤30 mg/day	52 (52.0)	25 (50.0)	27 (54.0)	26 (51.0)
>30 mg/day	48 (48.0)	25 (50.0)	23 (46.0)	25 (49.0)
Disease duration, days, mean (SD)	306.8 (563.5)	258.4 (500.7)	364.7 (569.9)	255.2 (435.5)
Signs or symptoms of GCA,[a] n (%)	37 (37.0)	23 (46.0)	20 (40.0)	24 (47.1)
Symptoms of PMR,[b] n (%)	59 (59.0)	32 (64.0)	30 (60.0)	35 (68.6)
Erythrocyte sedimentation rate, mm/h, mean (SD)	24.6 (18.7)	20.8 (18.1)	28.8 (25.4)	24.2 (18.2)
Diagnosis by positive temporal artery biopsy, n (%)	57 (57.0)	34 (68.0)	36 (72.0)	29 (56.9)
Diagnosis by positive imaging, n (%)	50 (50.0)	23 (46.0)	19 (38.0)	23 (45.1)

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
[a]Signs and symptoms of GCA: new-onset localised headache, scalp tenderness, or temporal artery tenderness, decreased pulsation, or jaw or mouth claudication.
[b]Symptoms of PMR: morning stiffness and/or pain in the shoulder and/or hip girdles.
BMI: body mass index; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; SD: standard deviation

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The participant flow and disposition for patients in GiACTA is given in Appendix D, for both Part 1 and Part 2. A description of the statistical analyses of the Phase III GiACTA trial is shown in Table 8. (Note that a description of the statistical analyses of the Phase II NCT01450137 trial is given in Appendix K.)

Table 8: Summary of statistical analyses in Phase III GiACTA

Hypothesis objective	The primary analysis tested the null hypothesis (H0) that the proportion of patients in sustained remission at Week 52 on TCZ in combination with a 26-week GC taper regimen was the same as the proportion of patients in sustained remission at Week 52 on placebo in combination with a 26-week GC taper regimen. The alternative hypothesis (H1) was that the proportion of patients in sustained remission at Week 52 on TCZ in combination with a 26-week GC taper regimen was not the same as the proportion of patients in sustained remission at Week 52 on placebo in combination with a 26-week GC taper regimen.
Statistical analysis	The primary and key secondary endpoints were tested at a 1% overall significance level ($\alpha = 0.01$) against two-sided alternatives. There were two independent hierarchies for the TCZ dose families for which the overall alpha-level was equally divided in order to correct the type I error rate for multiple comparisons. Both hierarchies tested the treatment comparisons in a fixed sequential order to further control for multiplicity. • Hierarchy 1 tested the primary endpoint for superiority of TCZ QW + 26-week GC taper versus placebo + 26-week GC taper, followed by the key secondary endpoint for non-inferiority of TCZ QW + 26-week GC taper versus placebo + 52-week GC taper. • Hierarchy 2 tested the primary endpoint for superiority of TCZ Q2W + 26-week GC taper versus placebo + 26-week GC taper, followed by the key secondary endpoint for non-inferiority of TCZ Q2W + 26-week GC taper versus placebo + 52-week GC taper. Claims of statistical significance were not to be made on the key secondary endpoint if its preceding test for superiority did not yield a significant p-value (<0.005).
Sample size, power calculation	A sample size of 100 patients in the 162 mg TCZ QW + 26-week GC taper group and 50 patients in both the 162 mg TCZ Q2W + 26-week GC taper group and PBO QW + 26-week GC taper group (in combination with the 26-week GC taper group) ensured at least 90% power to detect a difference in the proportion of patients in sustained remission at Week 52 for both TCZ arms versus placebo at an overall alpha level of 0.01 (2-sided). This assumed that the absolute difference in the proportion of patients who were in sustained remission at Week 52 was equal to 40% (assuming ρTCZ=70% versus ρ6-mCS=30%). In addition, 50 patients were also included in a PBO + 52 wk GC taper group.
Analysis populations	*Intent-to-treat population* The primary analysis population for all efficacy analyses was the intent-to-treat (ITT) population. The ITT population included all patients randomised into the study who received at least one TCZ/placebo injection. The treatment group for this population was defined according to the treatment assigned at randomisation by the IVRS. *Safety population* Analysis of safety data was based on the safety population. The safety population included all patients who received at least one administration of study drug and provided at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, or vital sign assessment). Patients were summarised according to the

	treatment they actually received.
Data management, patient withdrawals	Withdrawal patients who had a GCA flare prior to withdrawal were also classed as non-responders as this represents the true outcome had they remained in the study. Non-responder imputation was used for missing data. Patients who did not achieve remission within 12 weeks of baseline were also classed as non-responders in the primary analysis. All patients who received at least one administration of TCZ/PBO SC study drug, entered escape therapy, and received at least one dose of escape GC medication. Escape patients were classed as non-responders.
Sub-groups	The proportion of patients in remission and in sustained remission by visit was summarised descriptively for the following subgroups, with further investigation being carried out if required. Unless considered to be of major clinical relevance, subgroup analyses were only performed for subgroups where there was a minimum of 20% of patients from the overall population. • Disease onset at baseline (new-onset, relapsing) • Starting GC dose (5 mg intervals) was also summarised descriptively for this subgroup • Starting GC dose (≤30 mg/day, > 30 mg/day) • Previous history of remission, relapsing patients only (yes, no) • Positive imaging AND negative/no Temporal Artery Biopsy (TAB) AND no cranial symptoms at diagnosis (yes, no) • GCA diagnosis meeting the ACR criteria (yes, no) Where ACR 1990 criteria for diagnosis of GCA were defined as having 3 out of the following 5 symptoms: aged ≥ 50 years, ESR ≥ 50 mm/hour, new-onset localised headache, temporal artery abnormality, abnormal artery biopsy (i.e., positive TAB).

(Hoffman-La Roche Ltd. 2016)
GCA: giant cell arteritis; PBO: placebo; QW: every week; Q2W: every 2 weeks; TCZ: tocilizumab

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 9 provides a quality assessment of the Phase III GiACTA trial (Table 9). (Note that a quality assessment of the Phase II NCT01450137 trial is given in Appendix K.)

Table 9: Quality assessment results for the Phase III GiACTA trial

NICE Checklist Item	Phase III GiACTA Trial
Was randomisation carried out appropriately?	Yes (randomisation was done using an IVRS).
Was the concealment of treatment allocation adequate?	Yes (concealment was adequate as randomisation was done using an IVRS).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (the baseline demographics between the treatment groups were comparable).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes (investigators, patients and sponsor personnel were blinded to treatment assignment. Blinding was achieved by receiving either tocilizumab or matching tocilizumab placebo by SC injection once a week).
Were there any unexpected imbalances in drop-outs between groups?	No (there was no imbalance in dropouts between the treatment groups).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (all the outcomes mentioned in the study protocol were reported in the manuscript and study report; however, only those relevant for modelling cost-effectiveness are included in this dossier [*]).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes (ITT analysis was used for efficacy and safety outcome).

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
ITT: intent-to-treat; IVRS: interactive voice response system; SC: subcutaneous

B.2.6 Clinical effectiveness results of the relevant trials

The pivotal trial evaluating the efficacy and safety of tocilizumab in treating GCA was the GiACTA trial. The evidence from this trial forms the RCT evidence included in the cost-effectiveness modelling.

As mentioned in section B.2.2 List of relevant clinical effectiveness evidence, the Phase II NCT01450137 trial is not included in the cost-effectiveness modelling. Information on the

[*] NB: Not all reported outcomes were used to inform the economic model

Phase II NCT01450137 trial (methodology, results, etc.) is presented in Appendix K, in order to support the clinical efficacy and safety of tocilizumab in GCA.

GiACTA

In accordance with the proposed indication, the data reported in the clinical effectiveness section are based on the primary analysis (data cut-off 11th April 2016). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017) Of the 363 patients screened, 251 patients were randomised and 250 received the treatment to which they were assigned. The following patients were classed as non-responders in the primary analysis:

- patients who experienced a flare or who received escape therapy
- patients who did not adhere to the GC taper regimen (>100 mg additional glucocorticoids)
- patients who had two consecutive CRP elevations (≥ 1 mg/dL)
- patients who withdrew from the study prior to Week 52, or for whom a remission status could not be determined at Week 52

The ITT population was used for all primary efficacy analyses. P-values were quoted for superiority analyses only.

B.2.6.1 Disease remission

Primary endpoint

The Phase III GiACTA study met its primary endpoint: sustained remission at Week 52 (following induction and adherence to the protocol-defined GC taper) of both tocilizumab + GC groups compared with patients receiving placebo + 26-week GC.(Stone et al. 2017)

At Week 52, significantly more patients achieved sustained remission in both tocilizumab treatment groups compared with the placebo groups who received a short-course of glucocorticoid (GC) taper regimen (both $p<0.0001$); sustained remission achieved in 56.0% of patients in the TCZ QW + 26-week GC taper group and 53.1% of patients in the TCZ Q2W + 26-week GC taper group compared with 14.0% of patients in the PBO + 26 week group.(Stone et al. 2017)

The difference in the percentage of responders:

- between the tocilizumab QW and placebo group and
- between the tocilizumab Q2W and placebo group

were both significant, p<0.0001, which demonstrates tocilizumab's clinical and statistical superiority over placebo (Table 10). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Sensitivity analyses were performed on the primary endpoints to consider:

- only signs and symptoms of the disease
- GC-taper regimen adherence
- patient compliance and study completion

Results of the sensitivity analyses were consistent with those of the primary endpoint ITT analysis, for both tocilizumab groups (Table 10).(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 10: Proportion of patients achieving sustained remission at Week 52 in Phase III GiACTA trial (tocilizumab versus placebo + 26 week; ITT Population)

	PBO QW + 26-week GC Taper n = 50	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
ITT population			
Responders[a]	7 (14.0%)	56 (56.0%)	26 (53.1%)
Non-responders[a]	43 (86%)	44 (44.0%)	23 (46.9%)
Unadjusted difference in response rates (99.5% CI)		42.00 (18.00, 66.00)	39.06 (12.46, 65.66)
p-value (Cochran-Mantel-Haenszel) [b,c,d]		<0.0001	<0.0001

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
Patients were in sustained remission when they were responders from Week 12 to Week 52.
Elevated ESR attributed to GCA was reflected in flare by the investigator.
Patients who had received > 100 mg additional GC dosing from Week 12 to Week 52 were considered as not having adhered to the protocol-defined GC taper regimen.
[a] Patients in remission were classed as responders; Patients with elevated CRP whose next CRP value was elevated or missing were classed as non-responders; Patients not adhering to the protocol-defined GC taper were classed as non-responders.
[b] Superiority comparison uses pooled SE.
[c] Stratification factor, starting GC dose (≤ 30 mg/day, >30 mg/day) was included in the model.
[d] Analysis adjusted for the randomisation stratification factor applied at baseline.

Secondary endpoint

The GiACTA study met its key secondary endpoint: sustained remission at Week 52 (following induction and adherence to the protocol-defined GC taper) of both tocilizumab + 26-week GC taper groups compared with patients receiving placebo + 52-week GC taper.(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Both the tocilizumab QW and tocilizumab Q2W dose groups met non-inferiority criteria and subsequently superiority to placebo with regard to the key secondary endpoint.(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Sustained remission at Week 52 was achieved by 56.0% of patients in the tocilizumab QW group, 53.1% of patients in the tocilizumab Q2W group and 17.6% of patients in the placebo 52-week group (Table 11). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

The difference in the percentage of responders

- between the tocilizumab QW group versus the placebo 52-week group was 38.4% (99.5% CI: 17.9 to 58.8)
- and between the tocilizumab Q2W group versus the placebo 52-week group was 35.4% (99.5% CI: 10.4 to 60.4).

were both significant, ($p<0.0001$; $p=0.0002$). The lower boundaries of the 99.5% CIs for both tocilizumab dose groups were greater than the pre-specified non-inferiority margin of -22.5%, meeting the criteria for non-inferiority, and thus demonstrating tocilizumab's clinical and statistical superiority over placebo (Table 11).(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 11: Proportion of patients achieving sustained remission at Week 52 in Phase III GiACTA trial (tocilizumab versus placebo + 52 week; ITT Population)

	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
ITT population			
Responders[a]	9 (17.6%)	56 (56.0%)	26 (53.1%)
Unadjusted difference in response rates (99.5% CI)		38.35 (17.89, 58.81)	35.41 (10.41, 60.41)
p-value (Cochran-Mantel-Haenszel)[b,c,d]		<0.0001	0.0002

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
Patients were in sustained remission when they were responders from Week 12 to Week 52.
Elevated ESR attributed to GCA was reflected in flare by the investigator.
Patients who had received > 100 mg additional GC dosing from Week 12 to Week 52 were considered as not having adhered to the protocol-defined GC taper regimen.
[a] Patients in remission were classed as responders; Patients with elevated CRP whose next CRP value was elevated or missing were classed as non-responders; Patients not adhering to the protocol-defined GC taper were classed as non-responders.
[b] Superiority comparison uses pooled SE.
[c] Stratification factor, starting GC dose (≤ 30 mg/day, >30 mg/day) was included in the model.
[d] Analysis adjusted for the randomisation stratification factor applied at baseline.

B.2.6.2 Time to first GCA disease flare after disease remission

Time to first GCA disease flare after disease remission was a secondary endpoint.

The percentage of patients experiencing a flare by Week 52 was less for those who received tocilizumab QW or Q2W (23.0% and 26.5%, respectively) compared with patients who received placebo with either 26-week (68%) or 52-week (49%) GC taper (Table 12). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

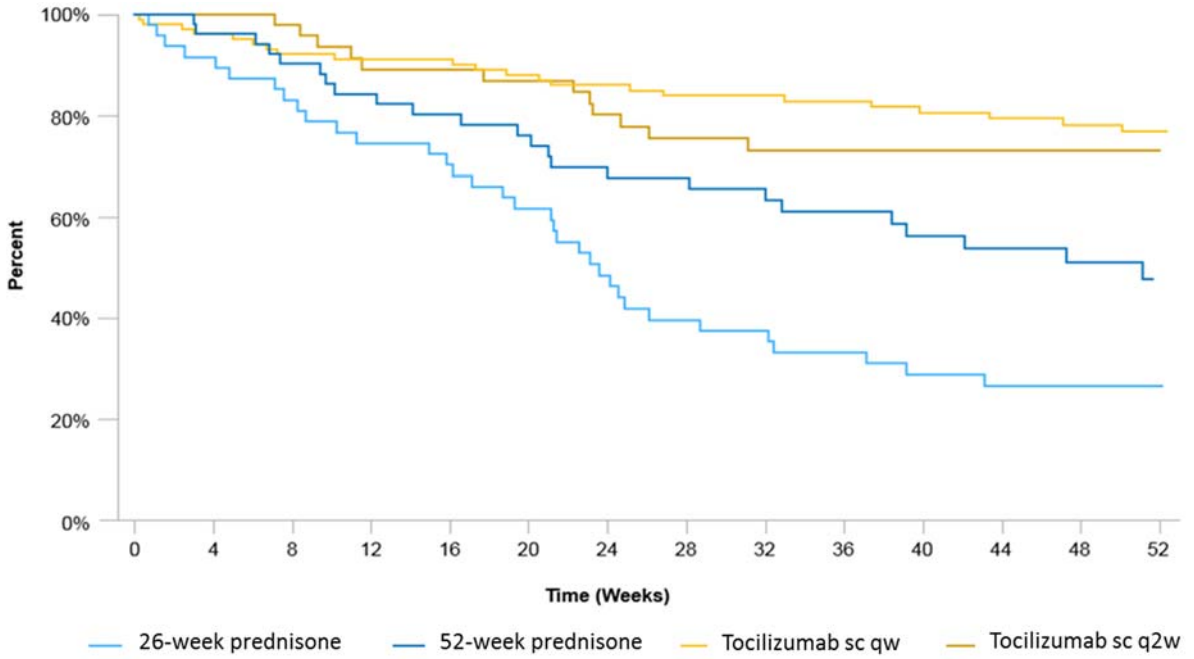
Tocilizumab treatment also significantly increased the time to first flare compared with placebo and the 26-week GC group ($p<0.0001$ for both doses) (Figure 3) indicating a statistically significant lower risk of flare in patients in both tocilizumab treatment groups versus placebo.(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 12: Time to first GCA disease flare (ITT population)

	PBO QW + 26 Week GC Taper (N=50)	PBO QW + 52 Week GC Taper (N=51)	TCZ QW + 26 Week GC Taper (N=100)	TCZ Q2W + 26 Week GC Taper (N=49)
Patients included in analysis	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
Patients with event (%)	34 (68.0%)	25 (49.0%)	23 (23.0%)	13 (26.5%)
Patients without event (%)	16 (32.0%)	26 (51.0%)	77 (77.0%)	36 (73.5%)
Time to event (days)				
Median	165	295	NE	NE
99% CI for Median	(120.0, 260.0)	(168.0, NE)	NE	NE
25% and 75%-percentile	92.0, NE	141.0, NE	NE	183.0, NE
Range	1 to 365	1 to 362	1 to 367	1 to 364
Stratified Analysis (vs PBO + 26 week taper)				
p-value			<0.0001	0.0001
Hazard Ratio			0.23	0.28
99% CI			(0.11, 0.46)	(0.12, 0.66)
Stratified Analysis (vs PBO + 52 week taper)				
p-value			0.0011	0.0316
Hazard Ratio			0.39	0.48
99% CI			(0.18, 0.82)	(0.20, 1.16)

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
CI: confidence interval; HR: hazard ratio; NE: not evaluable; PBO: placebo; QW: every week; Q2W: every 2 weeks; TCZ: tocilizumab
Patients who were never in remission are censored at Day 1.
Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.
The treatment groups are compared to Placebo using a Cox proportional hazards model adjusting for the stratification factor of starting GC dose

Figure 3: Kaplan-Meier plot of time to first flare (ITT population)



TCZ QW 26w	100	93	88	85	85	81	77	74	71	69	67	64	63	5
TCZQ2W 26w	49	47	45	40	40	39	35	32	30	30	29	26	24	2
PBO QW 26w	50	44	40	36	34	29	23	19	18	16	14	13	13	3
PBO QW 52w	51	48	44	41	38	35	32	30	28	25	22	17	15	0

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
PBO: placebo; QW: every week; Q2W: every 2 weeks; SC: subcutaneous; TCZ: tocilizumab

B.2.6.3 Annualised Relapse Rate

A summary of the annualised GCA relapse rate at Week 52 is shown in Table 13. Mean annualised relapse rates account for multiple flares observed in each patient and were highest in the PBO + 26 wk (1.74/year) and PBO + 52 wk (1.30/year) groups with lower relapse rates of 0.41/year in the TCZ QW + 26-week GC taper group and 0.67/year in the TCZ Q2W + 26-week GC taper group. The median annualised relapse rate was zero in the TCZ QW and TCZ Q2W treatment groups as fewer than 50% of patients in each of these groups had experienced a GCA disease flare by Week 52.(Hoffman-La Roche Ltd. 2016)

Table 13: Summary of annualised relapse rate at Week 52 in Phase III GiACTA (ITT population)

	PBO QW + 26 Week GC Taper (N=50)	PBO QW + 52 Week GC Taper (N=51)	TCZ QW + 26 Week GC Taper (N=100)	TCZ Q2W + 26 Week GC Taper (N=49)
Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)
Median	1.00	1.00	0.00	0.00
Range	0.0 - 12.6	0.0 - 10.3	0.0 - 4.0	0.0 - 4.0

(Hoffman-La Roche Ltd. 2016)

Annualised relapse rate is calculated as the number of flares between the first clinical assessment of GCA and the final clinical assessment prior to entry into Part 2, divided by the time period between the two days, multiplied by 365.25. First GCA assessment date is the one that occurs on or after the first treatment date. Number of flares is the actual number and includes all the flares that occurred multiple times (scheduled and unscheduled) at an analysis visit. (Hoffman-La Roche Ltd. 2016)

B.2.6.4 Exposure to glucocorticoid

Expected cumulative GC dose to Week 52 was calculated based on a patient's starting GC dose, the taper schedule (26-week or 52-week taper), and the assumption that the patient continued the taper without error. Median expected cumulative GC dose was, therefore, similar in the tocilizumab QW (1337.0 mg), tocilizumab Q2W (1442.0 mg), and placebo + 26-week (1337.0 mg) groups and higher in the placebo + 52-week (2607.5 mg) group Table 14). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Median actual GC treatment duration was 52 weeks (1 year) in all treatment groups, accounting for open-label GC taper, blinded GC/placebo as well as escape and commercial GC (for concomitant conditions). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

There was a statistically significantly lower cumulative GC dose to Week 52 in both tocilizumab treatment groups when compared to placebo in combination with a 26-week or 52-week GC taper period. (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

- Median total cumulative GC dose was identical in the TCZ QW and TCZ Q2W + 26-week GC taper groups (1862 mg)
- However, as a result of the increased use of escape glucocorticoid therapy (and longer GC taper period in the PBO+52 week group), median total cumulative GC dose was higher in the PBO+26-week (3296 mg) and PBO+52-week (3817.5 mg) groups

- The associated stratified analysis p-values for TCZ versus placebo in combination with a 26-week GC taper were p <0.0001 for the TCZ QW + 26-week GC taper group and p=0.0003 for the TCZ Q2W + 26-week GC taper group indicating a statistically significantly lower cumulative GC dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups when compared to placebo in combination with a 26 week GC taper period

- Corresponding stratified analysis p values for the TCZ QW and TCZ Q2W + 26-week GC taper groups versus placebo in combination with a 52 week GC taper were both p<0.0001 indicating a statistically significantly lower cumulative GC dose to Week 52 in both the TCZ QW and TCZ Q2W treatment groups compared to placebo in combination with a 52 week GC taper

The identical actual median cumulative GC dose reported in the tocilizumab groups reflects the fact that more than 50% of patients in each of the tocilizumab groups met the primary endpoint and adhered to the protocol defined GC taper. The mean actual cumulative dose is higher in the tocilizumab Q2W group, which is evidence of the very high doses of escape GC recorded for some escape patients in that treatment group. (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

A plot of the cumulative GC dose over time based on observed data is shown Figure 4. The curves of median cumulative GC dose were similar in all tocilizumab and placebo treatment groups up to approximately Week 22 (which corresponds to the time at which the blinded GC taper approaches 0 mg/day for these groups between Weeks 21 and 27, depending on starting GC dose). After Week 22, the curves for the tocilizumab QW and tocilizumab Q2W treatment groups start to plateau reflecting the fact that patients in these treatment groups received little additional GC, as per the study design and owing to the lower proportion of patients experiencing flare. In the placebo groups, however, the median cumulative GC dose continued to increase throughout the study with the highest median cumulative GC dose being observed in the placebo + 52 -week group, partly due to study design but also as a result of the number of escape patients receiving increased steroid doses. (Hoffman-La Roche Ltd. 2016)

In post hoc analyses, the percentages of patients who received open-label prednisone as escape therapy were 23% in the TCZ QW + 26-week GC taper group, 33% in the TCZ Q2W + 26-week GC taper group, 74% in the PBO QW + 26-week GC taper group, and 55% PBO QW + 56-week GC taper group.(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Duration of Glucocorticoid Use

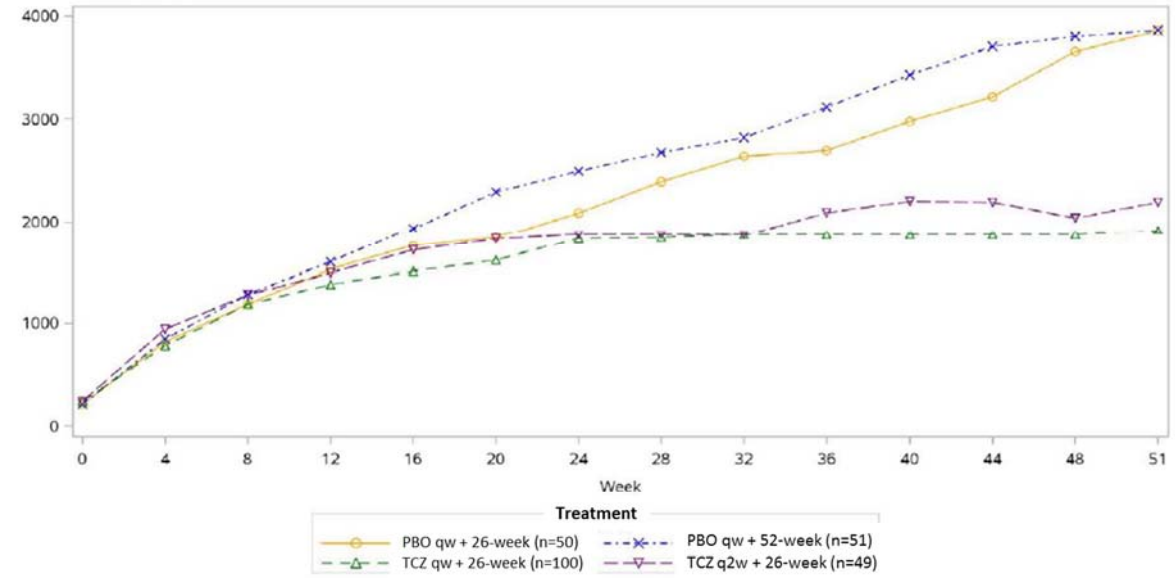
Analysis of glucocorticoid use to Week 52 (including only active glucocorticoid use, and where dose records of 0 mg are excluded from the summary) showed that although median treatment duration at each time point to Week 51 (Study Week 52) was comparable in all treatment groups, this should be taken in the context of the decreasing number of patients particularly in the TCZ treatment groups still receiving active glucocorticoid treatment after Week 19 (end of the GC taper period). The summary of glucocorticoid use over time shows a large decrease in evaluable patients, n, between Week 19 and Week 25 in both TCZ groups reflecting the large number of patients that adhered to the GC taper in these groups, as this is when their active GC consumption stops. Consequently, the summary also shows that a lower proportion of patients in the TCZ treatment groups remained on active GC to Week 52 compared with the placebo groups. By Week 51 glucocorticoids were being received by 18/100 (18%) of patients in the TCZ QW + 26-week GC taper group and 10/49 (20%) of patients in the TCZ Q2W + 26-week GC taper group compared with 28/50 (56%) of patients in the PBO QW + 26-week GC taper group and 27/51 (53%) of patients in the PBO QW + 52-week GC taper group. (Hoffman-La Roche Ltd. 2016)

Table 14: Exposure to GC in Phase III GiACTA

	PBO QW + 26-week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Treatment duration (days)				
Mean (SD)	337.2 (74.2)	338.4 (78.4)	325.3 (91.4)	325.7 (80.0)
Median	364.0	364.0	363.0	363.0
Range	50 - 389	56 - 366	9 - 366	18 - 365
Number of doses				
Mean (SD)	344.8 (103.4)	338.3 (78.6)	329.3 (106.1)	344.9 (126.8)
Median	363.0	363.0	362.0	363.0
Range	56 - 854	56 - 390	8 - 860	18 - 1020
Total expected cumulative dose (mg)				
Mean (SD)	1522.78 (540.1)	2694.52 (732.88)	1500.8 (567.75)	1606.93 (571.83)
Median	1337	2607.5	1337	1442
Range	952.0–2632.0	822.5–3902.5	350.0–2632.0	332.5–2632.0
Actual cumulative dose (mg)				
Mean (SD)	3765.19 (2022.45)	4199 (2291.32)	2097.84 (1248.45)	2447 (1827.31)
Median	3296	3817.5	1862	1862
Range	932.0–9777.5	822.5–10697.5	630.0–6602.5	295.0–9912.5
95% CI of the Median	2729.5, 4023.5	2817.5, 4425.5	1582.0, 1942.0	1568.0, 2239.5
P-Value				
Placebo QW + 26 Week Prednisone Taper		0.8297	**<0.0001**	0.0003
Placebo QW + 52 Week Prednisone Taper			**<0.0001**	<.0001

(Hoffman-La Roche Ltd. 2016)
Van Elteren's test was used to calculate p-values. Analysis was stratified by starting GC dose (<=30 mg/day, >30 mg/day). For any records of missed tablets from the protocol-defined GC taper, the missed tablet(s) will be assumed to be the minimum
dose tablet(s) available from that pack. Patients who received increased GC due to entering escape therapy will be included in their original treatment group. Expected cumulative dose is based on a patient's starting GC dose in the taper and assumes they continued the taper without error. Actual cumulative dose is based on actual records of GC taken and includes all escape therapy and commercial GC as well as taper GC.

Figure 4: Plot of median cumulative GC dose by visit and treatment group to Week 52 (GiACTA ITT Population)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s), were assumed to be the minimum dose tablet(s) available from that pack.
Patients who received increased prednisone due to entering escape therapy were included in their original treatment group.
Patient who withdrew were excluded from the summaries for subsequent visits.
Prednisone records were reported up to study date 364. Week 0 to week 51 includes the 52 weeks of Part 1 prednisone exposure.

(Hoffman-La Roche Ltd. 2016)

B.2.6.5 Health related quality of life

Patients in both tocilizumab groups showed no deterioration from baseline on any of the four instruments evaluated for HRQoL. Despite not all results reaching statistical significance, this indicates an overall improvement in HRQoL with tocilizumab compared with placebo plus GC.

Change in EQ-5D

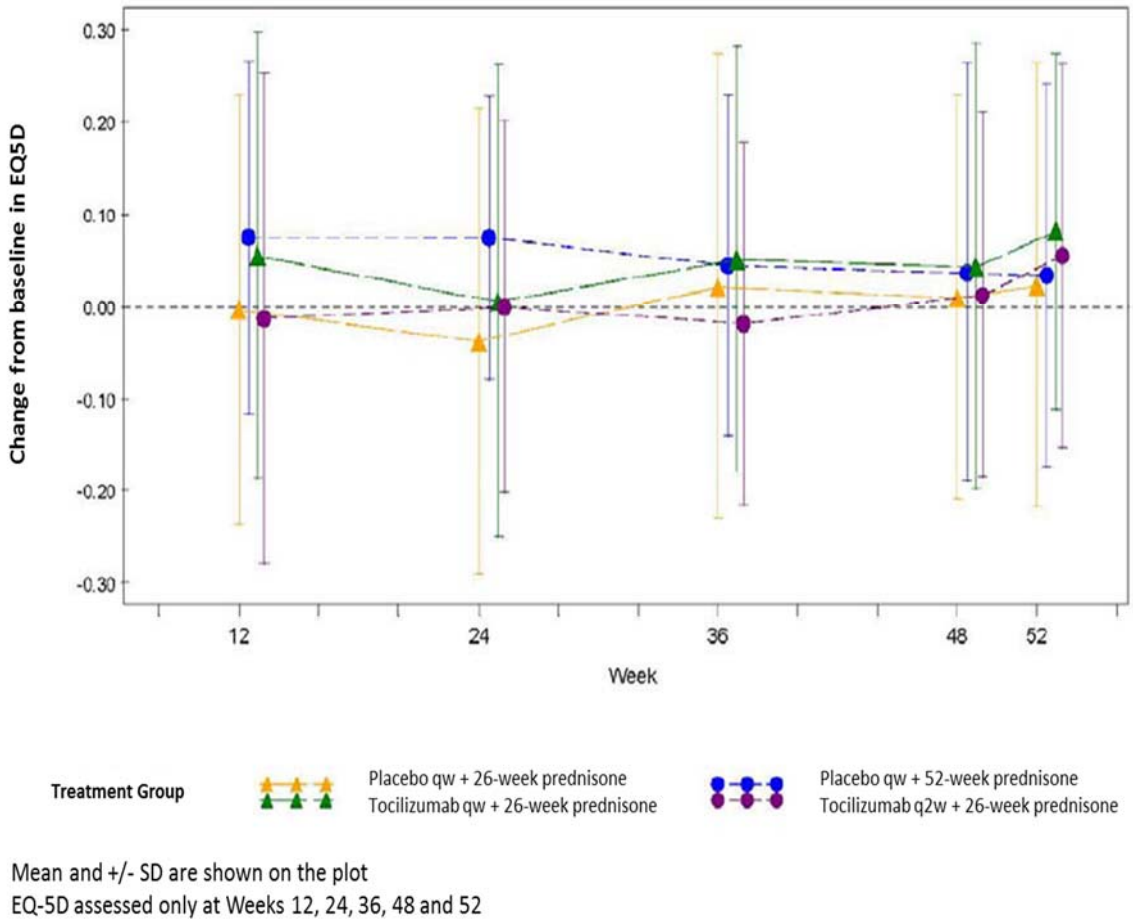
There was no notable deterioration in EQ-5D scores in any treatment group over the study period. Mean (SD) change from baseline scores at Week 52 were 0.10 (0.198) in the tocilizumab QW group, 0.05 (0.215) in the tocilizumab Q2W group, 0.07 (0.293) in the placebo 26-week GC regimen group and -0.02 (0.159) in the placebo 52-week GC regimen group (Figure 5, Table 15). (Hoffman-La Roche Ltd. 2016)

Table 15: Change from baseline in EQ-5D by visit and treatment group, ITT Population

	PBO QW + 26-week GC taper (n=50)	PBO QW + 52-week GC taper (n=51)	TCZ QW + 26 week GC taper (n=100)	TCZ + 26-week GC taper (n=49)
Value at visit				
n	11	18	60	26
Mean	0.77	0.78	0.86	0.83
SD	0.272	0.165	0.131	0.132
Median	0.80	0.75	0.85	0.80
Min, Max	0.16, 1.00	0.52, 1.00	0.52, 1.00	0.59, 1.00
Change from baseline				
n	11	17	60	26
Mean	0.07	-0.02	0.10	0.05
SD	0.293	0.159	0.198	0.215
Median	0.00	0.00	0.05	0.00
Min, Max	-0.53, 0.59	-0.48, 0.20	-0.20, 0.81	-0.20, 0.74

(Hoffman-La Roche Ltd. 2016)

Figure 5: Mean change from baseline in EQ-5D scores to Week 52



(Hoffman-La Roche Ltd. 2016)

Patients' Global Assessment

The mean change in the patients' global Visual Analogue Scale from baseline was analysed as a secondary endpoint. All treatment groups (placebo and TCZ) showed a decline (indicating improvement) from baseline over the 52-week study period, with the decline being more pronounced in the TCZ treatment groups. The decline in the TCZ Q2W + 26-week GC taper group was statistically significant when compared to both placebo groups (26-week: p=0.0059; 52-week p=0.0081). The TCZ QW + 26-week GC taper group also showed a numerical improvement when compared to either placebo group but the difference did not reach the pre-specified threshold of 0.01 for statistical significance. (Table 16) (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 16: Patient's global VAS assessment change from baseline at Week 52

	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
n	34	42	88	46
Least Square Means (LSM)	-3.4	-7.2	-19	-25.3
Differences in Least Square Means vs PBO QW + 26-week Prednisone Taper			-15.6	-21.9
99% CI for Difference in LSM			(-34.3,3.1)	(-42.4,-1.4)
P-value			0.0312	0.0059
Differences in Least Square Means vs PBO QW + 52-week Prednisone Taper			-11.8	-18.2
99% CI for Difference in LSM			(-27.2,3.6)	(-35.8,-0.5)
P-value			0.0476	0.0081

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
Repeated measures model used for analysis included the following covariates and interactions: treatment, starting GC dose (≤30 mg/day, >30 mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction. n represents patients included in the model.

Short Form-36 (SF-36)

Analysis of the Short Form-36 (SF-36) health survey was also a secondary study endpoint in GiACTA. The change from baseline to Week 52 of the SF-36 Physical Component Score showed a numeric improvement in both of the TCZ groups, while both placebo groups showed a slight worsening. However, only the difference between the TCZ QW + 26-week GC taper group and the PBO 52 week group reached the level for statistical significance (p=0.0024). The change from baseline to Week 52 in the Mental Component Score showed a numeric improvement in all treatment groups (placebo and TCZ). There were no significant differences between the treatment arms (p<0.01) (Table 17). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 17: Analysis of the change from baseline in SF-36 Mental Component Score and Physical Component Score at Week 52 in Phase III GiACTA

	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Mental Component Score				
n	33	41	85	46
Least Square Means (LSM)	6.67	2.84	7.28	6.12
Differences in Least Square Means vs PBO QW + 26-week GC Taper			**0.61**	**-0.56**
99% CI for Difference in LSM			(-5.86,7.07)	(-7.64,6.53)
P-value			0.8067	0.8374
Differences in Least Square Means vs PBO QW + 52-week GC Taper			**4.44**	**3.27**
99% CI for Difference in LSM			(-0.69,9.56)	(-2.59,9.14)
P-value			0.0252	0.1468
Physical Component Score				
n	33	41	85	46
Least Square Means (LSM)	-0.28	-1.49	4.1	2.76
Differences in Least Square Means vs PBO QW + 26-week GC Taper			**4.38**	**3.04**
99% CI for Difference in LSM			(-1.58,10.34)	(-3.43,9.51)
P-value			0.057	0.2218
Differences in Least Square Means vs PBO QW + 52-week GC Taper			**5.59**	**4.25**
99% CI for Difference in LSM			(0.86,10.32)	(-1.14,9.64)
P-value			0.0024	0.0412

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
Repeated measures model used for analysis included the following covariates and interactions: treatment, starting GC dose (≤30 mg/day, >30 mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction. No imputation of missing PCS and MCS has been performed. Post-escape SF-36 data will be set to missing. n represents patients included in the model.

FACIT-Fatigue (FACIT-F)

Changes in FACIT-Fatigue were analysed as an exploratory patient-reported outcome measure. In comparison to the placebo groups, numerically higher mean changes from baseline were observed in the FACIT-F scores at Week 52 for both TCZ groups (QW: +5.61±10.12; Q2W: +1.81±8.84; PBO 26-week: 0.26±10.70; PBO 52-week: -1.63±6.75). No

statistical testing was performed due to the exploratory nature of the endpoint (Table 18). (Hoffman-La Roche Ltd. 2016)

Table 18: Change from baseline in FACIT Fatigue score at Week 52 in Phase III GiACTA

Change from Baseline in FACIT Fatigue Score at Week 52	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Change from Baseline				
n	11	17	59	26
Mean	0.26	-1.63	5.61	1.81
SD	10.702	6.753	10.115	8.836
Median	1	0	2	1
Min, Max	-27.0, 18.0	-17.0, 9.0	-13.0, 30.0	-16.0, 27.0
(Hoffman-La Roche Ltd. 2016) No imputation used for missing data. Post-escape FACIT-Fatigue scores will be set to missing.				

B.2.6.6 Longer term disease control

As described in section B.2.3.1 Phase III GiACTA trial design, after the 52-week double-blind treatment period in the GiACTA study, all patients entered the 104-week open-label extension/long-term follow-up (Part 2) of the study – this is still on-going. This preliminary data has not yet been published (expected 2018). (Roche Products Ltd. 2017) Note that as this part of the study is incomplete, the data have not been used for any economic extrapolation.

A subset of patients (n=88) that had data up to at least Week 100 in Part 2 of the study have been evaluated in an exploratory manner (unpublished data). (Roche Products Ltd. 2017)

Patient data have been analysed based on response to treatment in Part 1 of the study:

- Part 1 responders (those who met the primary endpoint) were followed off tocilizumab treatment to assess the maintenance of response enabled by one year of tocilizumab treatment
- Part 1 non-responders were analysed to determine whether they can attain remission following treatment with open-label tocilizumab QW during Part 2 of the study.

Both groups were evaluated to assess the effectiveness of open-label TCZ QW treatment in bringing about remission following a GCA flare.

At the time of the Part 1 data cut (11 April 2016), there were 88 patients who had reached the Week 100 visit or beyond, with some patients having participated up to Week 136. As such, the duration of follow-up in Part 2 ranges from 48 to 84 weeks. Data for patients who did not reach the Week 100 visit due to withdrawal from the study or death during Part 2 are also included in the analysis. The patients included in the data cut were equally distributed across the four Part 1 treatment groups and the baseline demographics were representative of the total GiACTA patient population. The participant flow in Part 2 of GiACTA is shown in **Error! Not a valid bookmark self-reference.**]

Figure 6: Disposition of patients in Part 2 of GiACTA by treatment assignment from Part 1

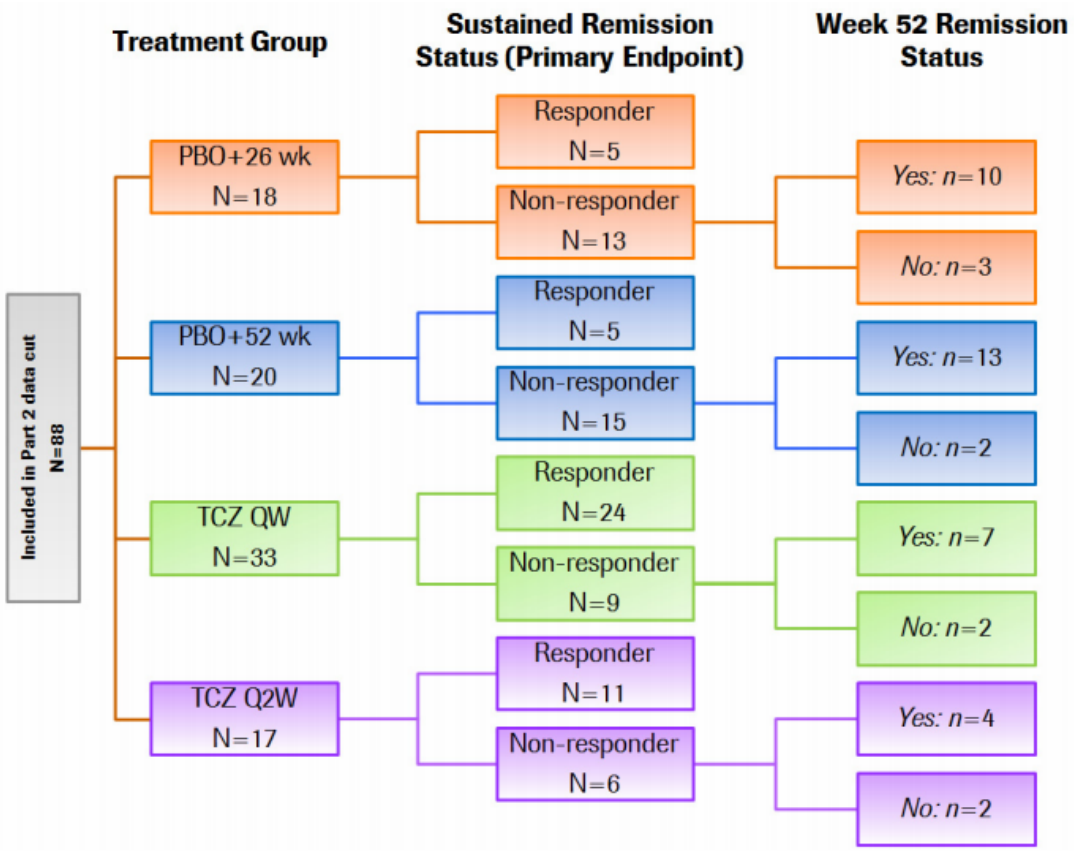
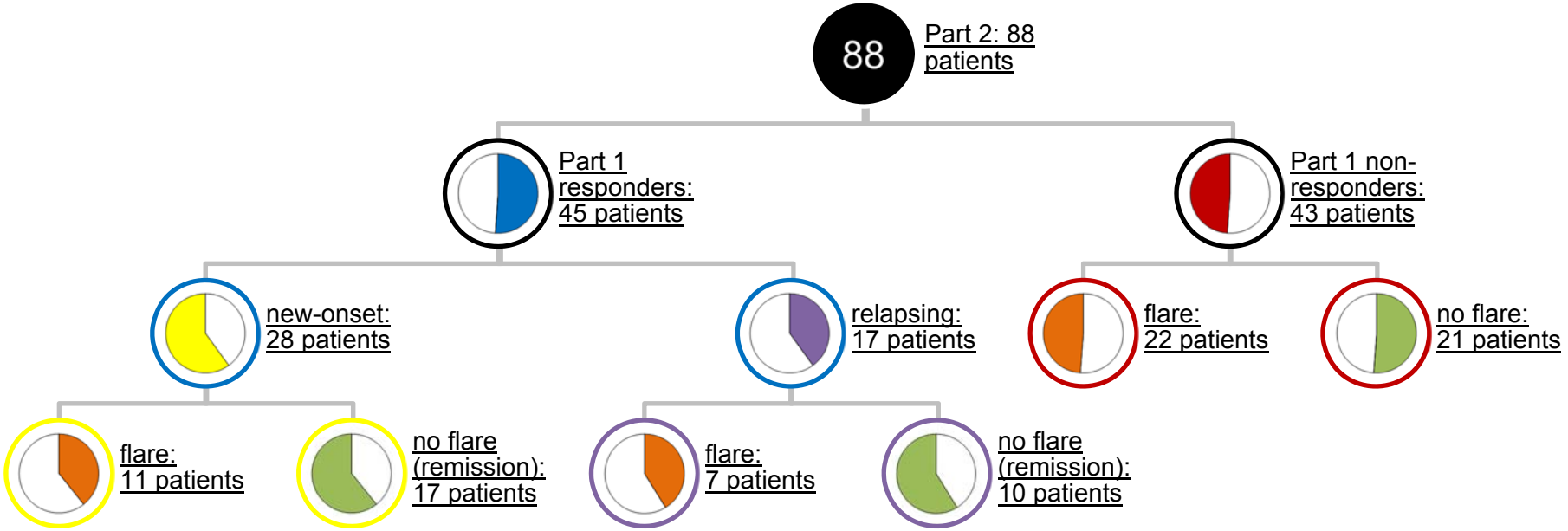


Figure 7: Patient disposition in Part 2 of GiACTA by response



Of the 88 patients evaluated at the time of the data cut, 45 met the primary endpoint during Part 1 of the study (were in sustained remission from Week 12 to Week 52) and 43 patients were non-responders in Part 1 of the study. Of the 43 non-responders, 34 were in remission at the Week 52 visit due to treatment with escape GC; the remaining nine patients were not in remission at the Week 52 visit.

Part 1 responders: maintenance of response in Part 2

Of the 45 patients who met the primary endpoint in Part 1 of the study, 27 remained in remission throughout available follow-up during Part 2. GCA flares were observed in 18 patients.

The 35 TCZ-treated patients who met the primary endpoint in Part 1 were followed to see how many of them relapsed during Part 2 of the study.

- 16 patients (46%) flared during Part 2, suggesting that treatment with TCZ is required beyond 1 year
- More patients who previously received TCZ Q2W in Part 1 experienced a GCA flare compared to those who previously received TCZ QW during Part 1 (Table 19). This is consistent with the concept that the TCZ QW regimen may be more effective at suppressing disease activity than the TCZ Q2W dose following one year of treatment.

The [redacted]. However, there was [redacted]. Additionally, [redacted].

Table 19: Part 1 Responders: Patients who flared during Part 2

Part 1 Treatment group	n	Patients with flares (%)	Patients without flares (%)
PBO QW + 26 week GC taper	5	1 (20%)	4 (80%)
PBO QW + 52 week GC taper	5	1 (20%)	4 (80%)
TCZ QW + 26 week GC taper	24	8 (33%)	16 (67%)
TCZ Q2W + 26 week GC taper	11	8 (73%)	3 (27%)

Part 1 non-responders: relapses in Part 2

Of the 43 patients who did not meet the primary endpoint in Part 1 of the study:

- 22/43 (51%) experienced disease flare in Part 2, of which 16/22 (73%) were receiving treatment for their GCA at the time of flare
- 21/43 (49%) did not experience disease flare in Part 2.

41 of the 43 patients had experienced a flare during Part 1: these patients can be considered as relapsing. (See **Error! Not a valid bookmark self-reference.**).

Table 20: Part 1 Non-responders: patients who flared during Part 2

Subgroup	n	Part 1 Treatment group	n	Patients with flares (%)	Patients without flares (%)
Part 1 Non-responders: in Remission at Week 52	34	PBO QW + 26 week GC taper	10*	3 (30%)	7 (70%
		PBO QW + 52 week GC taper	13	6 (46%)	7 (54%)
		TCZ QW + 26 week GC taper	7	6 (86%)	1 (14%)
		TCZ Q2W + 26 week GC taper	4	4 (100%)	0
Part 1 non-Responders: Not in Remission at Week 52	9	PBO QW + 26 week GC taper	3	0	3 (100%)
		PBO QW + 52 week GC taper	2	2 (100%)	0
		TCZ QW + 26 week GC taper	2	0	2 (100%)
		TCZ Q2W + 26 week GC taper	2	1 (50%)	1 (50%)

Flares in Part 2 by patient subtype

More GCA flares were observed in Part 2 in those patients who had relapsing disease upon entry into the GiACTA trial than those with new-onset disease.

Of the patients who flared while being treated with open-label tocilizumab in Part 2, the majority were patients who had relapsing disease upon entry into Part 1 of the study.

B.2.6.7 Treatment of flare in Part 2:

This preliminary data has not yet been published (expected 2018). (Roche Products Ltd. 2017) Note that as Part 2 of the study is incomplete, the data have not been used for any economic extrapolation.

A total of 40/88 patients had a GCA flare during Part 2 of the study and were treated with open-label TCZ (either alone or in combination with GC or with MTX) or with GC alone.

Treatment was defined as medication initiation or changes in medication dose that occurred between the flare study day and within one week after the study visit at which the flare was reported. Patients with a GCA flare were treated as follows:

- [redacted] patients were treated with open-label TCZ alone;
- [redacted] patients were treated with open-label TCZ plus GC;
- [redacted] patient was treated with open-label TCZ plus MTX;
- [redacted] patients were treated with GC alone.

Once [redacted].

[redacted].

B.2.7 Subgroup analysis

The proportion of patients in remission and in sustained remission by visit was summarised descriptively for the following subgroups, with further investigation being carried out if required. Unless considered to be of major clinical relevance, subgroup analyses were only performed for subgroups where there was a minimum of 20% of patients from the overall population. (Hoffman-La Roche Ltd. 2016)

- Disease onset at baseline (new-onset, relapsing)
- Starting GC dose (≤30 mg/day, >30 mg/day)
- Previous history of remission, relapsing patients only (yes, no)
- Positive imaging AND negative/no Temporal Artery Biopsy (TAB) AND no cranial symptoms at diagnosis (yes, no)
- GCA diagnosis meeting the ACR criteria (yes, no)

GCA disease characteristics within each of these subgroups were generally consistent with those of the overall patient population, with any observed differences between the treatment groups assumed to be due to the small sample sizes. (Hoffman-La Roche Ltd. 2016)

Since the results of the subgroups were consistent with the results of the overall ITT population (Hoffman-La Roche Ltd. 2016), subgroup analyses were not included in the economic model.

New-onset GCA was defined as GCA diagnosed within 6 weeks of the baseline visit. Relapsing GCA was defined as GCA diagnosed >6 weeks before the baseline visit and previous treatment with ≥ 0 mg/day GC (or equivalent) for at least 2 consecutive weeks at any time. The study protocol limited enrollment of relapsing patients to 70% to enable a sufficient number of new-onset patients to be enrolled. The actual enrollment of patients with relapsing GCA was 53%, while 47% of patients enrolled had new-onset GCA. There was a

balanced distribution of new-onset or relapsing patients in each of the treatment groups. (Hoffman-La Roche Ltd. 2016)

Analyses of baseline disease characteristics for the new-onset and relapsing patient subgroups showed that in new-onset patients, median duration of GCA at baseline was 33 days in the TCZ QW + 26-week GC taper group, 28 days in the TCZ Q2W + 26-week GC taper group, 33 days in the PBO QW + 26-week GC taper group and 26 days in the PBO QW + 52-week GC taper group. (Hoffman-La Roche Ltd. 2016)

In relapsing patients, median duration of GCA at baseline was 326 days in the TCZ QW + 26-week GC taper group, 229 days in the TCZ Q2W + 26-week GC taper group, 477 days in the PBO QW + 26-week GC taper group and 204 days in the PBO QW + 52-week GC taper group. (Hoffman-La Roche Ltd. 2016)

B.2.8 Meta-analysis

GiACTA was the only randomised clinical study identified in the SLR to be relevant to the decision problem, therefore a meta-analysis is not feasible.

Moreover, the efficacy data from the Phase III GiACTA study and the Phase II NCT01450137 study was not pooled because of differences in treatment regimens and study designs, as described in section B.2.2 List of relevant clinical effectiveness evidence.

The detailed efficacy results from the Phase III GiACTA trial are included in this main document; the results from the Phase II NCT01450137 study are presented in Appendix K.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were conducted since neither an indirect treatment comparison or network meta-analysis were not deemed to be feasible. Even if one were feasible, its benefit would be unclear given the robustness of evidence from the GiACTA trial to address the decision problem, and the limited use of immunosuppressants, biological therapies or other therapies in clinical practice in the UK.

The final NICE scope for this appraisal states tocilizumab is to be compared to established treatments.

Glucocorticoids

GCs are the mainstay of treatment for all patients. For the purpose of this submission, taking into account the scope of 'established treatments for GCA', we have excluded and not made comparisons with studies involving GC regimens that are not standard of care in the UK (e.g. methylprednisolone).

Immunosuppressants (including methotrexate)

The BSR guidelines state that the early introduction of MTX or alternative immunosuppressants should be considered as adjuvant therapy.

The published evidence for immunosuppressants shows inconsistent clinical benefit: a meta-analysis pooling the data of 3 randomised controlled trials demonstrated a modest reduction in relapse and GC exposure in the methotrexate-treated groups. (Mahr et al. 2007) However, a further meta-analysis of the same trials of methotrexate concluded there was no significant benefit. (Yates et al. 2014)

Additionally the trial designs of the trials mentioned in the above meta-analyses do not allow robust comparison with the GiACTA trial. Specifically, a robust and unbiased network meta-analysis is hindered by the following:

- Evolution in the diagnostic criteria for GCA over the previous 15 years;
- Population criteria differences: methotrexate studies only included newly-diagnosed patients; whereas the GiACTA trial included both newly-diagnosed and relapsed/refractory patients;
- Lack of standardised GC taper regimens across trials;
- Lack of consistent blinding to GC tapering regimen – risking bias;
- Inconsistent reporting of primary and secondary outcomes;
- No standardised definition of GCA remission/flare criteria

It should be noted that methotrexate was a permitted concomitant medication for GCA in the GiACTA trial (see Table 6). However, MTX was only taken by 10-16% of patients in each treatment arm (see Table 25).

Biological therapies

The BSR guidelines state that biological therapies still require further study, and are not yet recommended. Therefore, indirect or mixed treatment comparison of tocilizumab vs other biological therapies is not plausible.

B.2.10 Adverse reactions

The clinical safety data supporting this submission are derived primarily from the Phase III GiACTA trial, which evaluated the efficacy and safety of subcutaneous tocilizumab treatment compared with placebo in patients with GCA.

Supporting safety data are provided from a Phase II investigator-initiated trial (NCT01450137), studying intravenous tocilizumab in patients with newly diagnosed or relapsing GCA (Appendix F).

Analysis of adverse events reported in single case reports of patients with GCA treated with IV tocilizumab outside of clinical trials have not been reported here.

B.2.10.1 Phase III GiACTA trial adverse events

The safety profile was balanced across treatment groups and was consistent with that of previous tocilizumab trials. No deaths were reported during the main 52-week GiACTA study.

Most patients in the study experienced at least one AE, with the proportion of such patients ranging between 92.2% and 98.0% (Table 21). The AE rate was lower in both tocilizumab groups than in the placebo groups (872.0 AEs and 948.0 AEs per 100 patient years (PY) in the tocilizumab QW and Q2W groups, respectively, vs 990.8 and 1,011.2 AEs per 100 patient years in the placebo with 26-week GC and 52-week GC groups, respectively). The highest AE rate 100 PY occurred in the placebo with 52-wk course GC group. (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

- Grade 1 AEs were reported in 33% of patients in each of the tocilizumab groups, 32% of patients in the placebo + 26 wk group and 39% of patients in the placebo + 52 week group

- Grade 2 AEs were reported in 39% of patients in each of the tocilizumab groups, 40% of patients in the placebo + 26 wk group and 26% of patients in the placebo + 52 week group

- Grade 3 AEs were reported in 24% of patients in the tocilizumab QW group, 22% of patients in the TCZ Q2W + 26-week GC taper group, 22% of patients in the placebo + 26 week group and 26% of patients in the placebo + 52 week group

- Grade 4 AEs were reported in 4 patients: one patient in each of the four treatment groups
    - One patient in the tocilizumab QW group experienced Grade 4 pulmonary embolism (serious) on Study Day 142 and was hospitalised. The event was considered unrelated to blinded study treatment (tocilizumab or GC) by the investigator but related to concurrent illness. There was no change to study treatment as a result of the event. The patient received corrective treatment with acenocoumarol and the AE was considered resolved after 11 days
    - A patient in the tocilizumab Q2W group experienced Grade 4 thrombotic stroke (serious) on Study Day 254. The patient had been withdrawn from blinded tocilizumab study treatment (and blinded GC was interrupted) 13 days earlier due to the events of Grade 3 cellulitis and Grade 3 dry gangrene, both considered unrelated to treatment. The thrombotic stroke was considered unrelated to blinded study treatment by the investigator and all events resolved following corrective treatment
    - One patient in the placebo + 26 week group experienced Grade 4 arthralgia (serious) on Study Day 50 and was hospitalised. The event was considered related to blinded GC by the investigator. There was no change to study treatment and the AE resolved after 18 days following corrective treatment (nefopam, morphine)
    - A patient in the placebo + 52 week group experienced the Grade 4 AEs of chronic cardiac failure (Study Day 53, serious, unresolved), hepatic enzyme increased (Study Day 59, serious, resolved), both events which were considered related to blinded tocilizumab treatment by the investigator. In addition the patient experienced hypokalaemia (Study Day 97, serious, resolved), renal impairment (Study Day 97, serious, resolved) and (worsening) cardiac failure (Study Day 135, serious, unresolved), all of which were considered unrelated to blinded study treatment by the investigator
- No Grade 5 AEs (fatalities) were reported during Part 1 of the study

Fewer patients treated with tocilizumab experienced serious adverse events (SAEs) compared with patients in the placebo groups (15.0% and 14.3% in the tocilizumab QW and tocilizumab Q2W groups, respectively; 22.0% and 25.5% in the PBO + 26-week and PBO +

52-week groups, respectively). None of the SAEs were fatal. Of the SAEs, infections were similar in the tocilizumab and placebo groups. (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

The proportion of AEs leading to withdrawal from blinded tocilizumab/placebo treatment was 6% in the placebo+26-week group, 11% in the tocilizumab QW group and 10% in the tocilizumab Q2W group. There were no such events in the placebo + 52-week group. AEs leading to withdrawal of treatment which were considered related to blinded tocilizumab/placebo treatment by the investigator were as follows: (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

- Tocilizumab QW: grade 3 neutropenia (non-serious); grade 3 pneumonia haemophilus (serious) and grade 2 sepsis (non-serious); grade 3 pneumonia (serious); grade 3 herpes zoster (serious); grade 3 gastroenteritis (serious); grade 3 marginal zone lymphoma (non-serious)
- Tocilizumab Q2W: grade 3 rash (non-serious); grade 3 hypersensitivity (serious)
- Placebo + 26 week: grade 3 events of nasal inflammation (serious) and stomatitis (serious)

Table 21: Overview of adverse events in Phase III GiACTA

	PBO QW + 26-week GC taper (n=50)	PBO QW +52-week GC taper (n=51)	TCZ+26-week GC taper (n=100)	TCZ Q2W+ 26-week GC taper (n=49)
Adverse events (AE)				
Total number of patients with at least one AE	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
Total number of events	470	486	810	432
AE related to tocilizumab	21 (42.0%)	18 (35.3%)	52 (52.0%)	26 (53.1%)
AE related to GC	31 (62.0%)	25 (49.0%)	50 (50.0%)	30 (61.2%)
AE leading to dose modification/interruption	12 (24.0%)	17 (33.3%)	33 (33.0%)	10 (20.4%)
AE leading to dose modification/ interruption of blinded TCZ/placebo AE related to TCZ	10 (20.0%)	11 (21.6%)	28 (28.0%)	8 (16.3%)
AE with fatal outcome	0	0	0	0
Withdrawals				
Withdrawals from study due to an AE	2 (4.0%)	0	6 (6.0%)	3 (6.1%)
AE leading to withdrawal from treatment	6 (12.0%)	0	11 (11.0%)	6 (12.2%)
AE leading to withdrawal from blinded tocilizumab/placebo	3 (6.0%)	0	11 (11.0%)	5 (10.2%)
Serious Adverse Events (SAE)				
Total number of patients with at least one SAE	11 (22.0%)	13 (25.5%)	15 (15.0%)	7 (14.3%)
SAEs related to tocilizumab	4 (8.0%)	6 (11.8%)	4 (4.0%)	2 (4.1%)
SAEs related to GC	5 (10.0%)	4 (7.8%)	3 (3.0%)	1 (2.0%)
Deaths				
Total number of deaths	0	0	0	0

(Hoffman-La Roche Ltd. 2016)

AE: adverse event; NMSC: non-melanoma skin cancer; QW: every week; Q2W: every 2 weeks; SAE: serious adverse event; SMQN: Standardised MedDRA Query, narrow (scope)

Investigator text for AEs encoded using MedDRA version 19.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
* The events matching an anaphylactic reaction based on Sampson's criteria (eye pruritus, dyspnoea) were clinically not considered to be anaphylactic in nature. The investigator did not consider either of these events to be related to study drug and there were no modifications to either the tocilizumab or GC dose.

Common adverse events

The most common system organ class (SOC) for all-grade AE and Grade 3 AE reported was 'Infections and Infestations', followed by 'Musculoskeletal and Connective Tissue Disorders'.

The most common all-grade AEs (by preferred term) were headache (non-GCA related), nasopharyngitis, peripheral oedema, and arthralgia. Four Grade 4 events occurred in 4 patients (pulmonary embolism, thrombotic stroke, arthralgia and chronic cardiac failure with increased hepatic enzymes). (Hoffman-La Roche Ltd. 2016; Stone et al. 2017)

Table 22: Adverse events reported in ≥10% of patients in the Phase III GiACTA trial

	PBO QW + 26- week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Infections and infestations	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
Oral herpes	3 (6.0%)	2 (3.9%)	4 (4.0%)	5 (10.2%)
Upper respiratory tract infection	5 (10.0%)	7 (13.7%)	10 (10.0%)	6 (12.2%)
Bronchitis	5 (10.0%)	5 (9.8%)	8 (8.0%)	4 (8.2%)
Urinary tract infection	2 (4.0%)	4 (7.8%)	10 (10.0%)	4 (8.2%)
Nasopharyngitis	9 (18.0%)	13 (25.5%)	29 (29.0%)	12 (24.5%)
Musculoskeletal and connective tissue disorders	34 (68.0%)	32 (62.7%)	63 (63.0%)	28 (57.1%)
Back pain	7 (14.0%)	10 (19.6%)	14 (14.0%)	7 (14.3%)
Musculoskeletal pain	5 (10.0%)	2 (3.9%)	12 (12.0%)	6 (12.2%)
Pain in extremity	5 (10.0%)	5 (9.8%)	8 (8.0%)	5 (10.2%)
Muscle spasms	6 (12.0%)	4 (7.8%)	4 (4.0%)	6 (12.2%)
Arthralgia	11 (22.0%)	8 (15.7%)	13 (13.0%)	8 (16.3%)
Nervous System Disorder	23 (46.0%)	22 (43.1%)	43 (43.0%)	22 (44.9%)
Headache	16 (32.0%)	12 (23.5%)	27 (27.0%)	10 (20.4%)
Paraesthesia	5 (10.0%)	4 (7.8%)	4 (4.0%)	2 (4.1%)
Dizziness	6 (12.0%)	8 (15.7%)	6 (6.0%)	10 (20.4%)
General disorders and administrations site conditions	21 (42.0%)	14 (27.5%)	37 (37.0%)	25 (51.0%)
Fatigue	8 (16.0%)	3 (5.9%)	8 (8.0%)	5 (10.2%)
Asthenia	5 (10.0%)	0	5 (5.0%)	3 (6.1%)
Peripheral oedema	8 (16.0%)	6 (11.8%)	16 (16.0%)	12 (24.5%)

Skin and subcutaneous tissue disorders	17 (34.0%)	17 (33.3%)	33 (33.0%)	25 (51.0%)
Alopecia	3 (6.0%)	5 (9.8%)	5 (5.0%)	7 (14.3%)
Rash	4 (8.0%)	2 (3.9%)	7 (7.0%)	5 (10.2%)
Gastrointestinal disorders	19 (38.0%)	15 (29.4%)	36 (36.0%)	18 (36.7%)
Diarrhoea	8 (16.0%)	5 (9.8%)	12 (12.0%)	3 (6.1%)
Nausea	5 (10.0%)	4 (7.8%)	8 (8.0%)	2 (4.1%)
Respiratory, thoracic and mediastinal disorders	16 (32.0%)	17 (33.3%)	22 (22.0%)	11 (22.4%)
Oropharyngeal pain	5 (10.0%)	8 (15.7%)	7 (7.0%)	4 (8.2%)
Cough	7 (14.0%)	3 (5.9%)	6 (6.0%)	3 (6.1%)
Psychiatric disorders	13 (26.0%)	8 (15.7%)	12 (12.0%)	8 (16.3%)
Anxiety	6 (12.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
Vascular disorders	13 (26.0%)	9 (17.6%)	23 (23.0%)	13 (26.5%)
Hypertension	4 (8.0%)	4 (7.8%)	12 (12.0%)	6 (12.2%)

(Hoffman-La Roche Ltd. 2016)
QW: every week; Q2W: every 2 weeks
Percentages are based on n in the column headings.

B.2.10.2 Adverse events of special interest (AESI)

AESI for tocilizumab were predefined on the basis of safety concerns for the GCA population, findings from clinical studies in rheumatoid arthritis, and the safety profile of other biologic agents used to treat rheumatoid arthritis. Adverse events of special interest (AESIs) were defined using published Standard MedDRA Queries (SMQs) or Adverse Event Grouped Terms (AEGTs) defined by Roche Drug Safety. These included but were not limited to the following: infections, opportunistic infections, malignancies, hepatic events, hypersensitivity, ISRs, anaphylactic reactions, stroke, myocardial infarction, gastrointestinal perforations, bleeding events, and demyelinating events. (Hoffman-La Roche Ltd. 2016)

There were no reports of serious hepatic events, serious myocardial infarction events, serious gastrointestinal perforation events, serious bleeding events, or serious demyelinating AEs during the 52 week double-blind phase of the study. (Hoffman-La Roche Ltd. 2016)

Infections

There were no marked differences in the overall incidence of patients with infections between TCZ QW + 26-week GC taper (75%), TCZ Q2W + 26-week GC taper (74%), PBO QW + 26-week GC taper (76%) and PBO QW + 52-week GC taper (65%) treatment groups.

The most common types of infections across all treatment groups were nasopharyngitis upper respiratory tract infection, bronchitis and urinary tract infection. Dose interruption because of infections occurred in 18% of patients in the TCZ QW + 26-week GC taper group, 14% of patients in the TCZ Q2W + 26-week GC taper group, 14% of patients in the PBO QW + 26-week GC taper group and 20% of patients in the PBO QW + 52-week GC taper group.

Serious infections were reported in 7% (7/100) of patients in the TCZ QW + 26-week GC taper group, 4% (2/49) of patients in the TCZ Q2W + 26-week GC taper group, 4% (2/50) of patients in the PBO QW + 26-week GC taper group, and 12% (6/51) of patients in the PBO QW + 52-week GC taper group.

The serious infection events of gastroenteritis and herpes zoster were both observed in 2 patients in the PBO QW + 52-week GC taper group. All other serious infections were single occurrences. Three urinary tract-related serious events (urinary tract infection, urosepsis and pyelonephritis) were reported in a single patient.

Serious infections resulted in the withdrawal of study treatment for five patients in the TCZ QW + 26-week GC taper group (pneumonia, chronic sinusitis, gastroenteritis, herpes zoster, and pneumonia haemophilus), one patient in the TCZ Q2W + 26-week GC taper group (cellulitis) and one patient in the PBO QW + 26-week GC taper group (pneumonia).

Opportunistic infections
Opportunistic infections were reported in two patients in the PBO QW+ 52- week GC taper group and one patient in the TCZ Q2W + 26-week GC taper group.

- A 78 year-old female in the PBO + 52-week GC taper group was reported with Grade 3 genital herpes zoster (serious) on Study Day 15. The patient received treatment for the event which was considered related to blinded study treatment (TCZ and GC) by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 27 days.

- A58 year-old female patient in the PBO QW + 52-week GC taper group was reported with Grade 1 cytomegalovirus infection (non-serious) on Study Day 325. The patient received treatment for the event which was considered unrelated to study treatment by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 19 days.

- A 70 year-old female in the TCZ Q2W + 26-week GC taper group was reported with Grade 1 oropharyngeal candidiasis (non-serious) on Study Day 8. The patient received treatment for the event, which was considered unrelated to study treatment by the investigator. The event was considered resolved after 15 days. On Study Day 197, the patient was reported with Grade 1 laryngitis fungal (non-serious) which resolved after 85 days. No treatment was given for this event which the investigator considered unrelated to study treatment. No changes were made to study treatment.

None of these opportunistic infections led to withdrawal of the patient from study treatment. A listing of patients with opportunistic infections based on the Roche AEGT basket is available and narratives are provided for all serious opportunistic infections.

In addition to the opportunistic infections defined by the Roche adverse event grouped terms basket, the Sponsor performed a manual review of potential opportunistic infections reported in the Infections and Infestations SOC ('herpes zoster' and 'tuberculosis').

Herpes zoster was reported in 5 patients (5.0%) in the TCZ QW + 26-week GC taper group, 2 patients (4.1%) in the TCZ Q2W + 26-week GC taper group, 0 patients in the PBO QW + 26-week group and 2 patients (3.9%) in the PBO QW + 52-week GC taper group. Most of these events were non-serious, Grade 2 events which did not result in a change to study treatment. Three patients were reported with a serious herpes zoster infection:

- A 74 year-old female in the PBO QW + 52-week GC taper group was reported with Grade 3 herpes zoster (serious) on Study Day 185. The patient received treatment for the event which was considered related to blinded study treatment (TCZ and GC) by the investigator. Blinded TCZ study treatment was interrupted and the event resolved after 56 days.

- A 65 year-old female in the PBO QW + 52-week GC taper group was reported with Grade 3 herpes zoster (serious) on Study Day 222. The patient received treatment for the event which was considered related to blinded TCZ study treatment by the investigator. Blinded study treatment was unchanged and the event resolved after 10 days.

- A 55 year-old male in the TCZ QW + 26-week GC taper group group was reported with Grade 3 herpes zoster (serious) on Study Day 136. The patient received treatment for the event which was considered related to blinded TCZ study treatment

by the investigator. Study treatment was discontinued due to the event which resolved after 90 days.

There were no reports of tuberculosis in GiACTA.

Malignancies

Malignancies were reported in three patients: one patient in each of the TCZ QW (marginal zone lymphoma), PBO QW+ 26-week GC taper (breast cancer, renal neoplasm) and PBO QW + 52-week GC taper (malignant melanoma) groups. Of these events, breast cancer and malignant melanoma were reported as SAEs.

- A 79 year-old male patient in the PBO QW + 26-week GC taper group was diagnosed with Grade 2 breast cancer on Study Day 246. The event was considered serious and unrelated to study treatment by the investigator. The patient was withdrawn from blinded TCZ study treatment due to this event. On Study Day 277, the patient was diagnosed with a Grade 3 renal neoplasm which the investigator considered non-serious and unrelated to study treatment.

- A 64 year-old male patient in the PBO QW + 52-week GC taper group was diagnosed with Grade 3 malignant melanoma on Study Day 315. The patient received treatment for the event which was considered serious and unrelated to study treatment by the investigator. No changes were made to blinded study treatment.

- A 76 year-old female patient in the TCZ QW + 26-week GC taper group was diagnosed with Grade 3 marginal zone lymphoma on Study Day 282. The event was considered non-serious and related to blinded TCZ study treatment by the investigator. The patient was withdrawn from blinded TCZ study treatment due to the event which was ongoing at the time of the completion of the 52-week double-blind phase of the study.

Serious stroke events

Serious stroke events were reported in one patient in the TCZ Q2W + 26-week GC taper group and one patient in the PBO QW + 52-week GC taper group.

- An 81 year-old male patient in the TCZ Q2W + 26-week GC taper group experienced a Grade 4 thrombotic stroke on Study Day 254. The patient received treatment for the event which resolved after 14 days and was considered unrelated to study

treatment by the investigator. The patient had previously discontinued blinded TCZ study treatment due to the separate Grade 3 AEs of cellulitis and dry gangrene.

- A 74 year-old female patient in the PBO QW + 52-week GC taper group experienced a Grade 3 transient ischemic attack (TIA) on Study Day 135. No treatment was given for the event which was considered serious but unrelated to study treatment. The TIA resolved after 1 day and the patient continued to receive blinded study treatment.

Anaphylaxis

No AEs as defined by the Anaphylactic Reaction SMQ Narrow were reported during the study. However, two AEs (eye pruritus, dyspnoea) were identified in a single patient using Sampson's criteria for anaphylaxis. (Sampson et al. 2006)

- A 58 year-old male patient in the TCZ Q2W + 26-week GC taper group experienced the Grade 1 eye pruritus on Study Day 9 and Grade 1 dyspnoea on Study Day 10. Neither event was considered related to study treatment by the investigator. No treatment was given for the events neither of which was reported as serious. The event of dyspnoea resolved after 1 day and the event of eye pruritus resolved after 290 days. No changes were made to blinded study treatment.

Hypersensitivity

Hypersensitivity reactions were those events which occurred during or within 24 hours of an injection (excluding ISRs) and that were not deemed "unrelated" to study treatment. A conservative approach was taken to identify potential hypersensitivity reactions and this retrieval included all AEs, regardless of whether or not they were consistent with hypersensitivity. Based on this retrieval, potential hypersensitivity reactions were observed in 11% (11/100) of patients in the TCZ QW + 26-week GC taper group, 12% (6/49) of patients in the TCZ Q2W + 26-week GC taper group, 12% (6/50) of patients in the PBO QW + 26-week GC taper group and 6% (3/51) of patients in the PBO QW + 52-week GC taper group. The most frequently reported events were in the SOC of Nervous System Disorders (mainly non-GCA headache and dizziness). With the exception of headache, reported in two patients in each of the TCZ QW and PBO QW + 26-week GC taper groups (and one patient in the PBO QW + 52-week GC taper group), dizziness reported in two patients in the TCZ QW + 26-week GC taper group (and one patient in each of the TCZ Q2W + 26-week GC taper and PBO QW + 26-week GC taper groups), back pain reported in two patients in the TCZ QW + 26-week GC taper group, hyperhidrosis reported in two patients in the TCZ QW + 26-week

GC taper group, and rash reported in two patients in the TCZ Q2W + 26-week GC taper group, all other hypersensitivity events were isolated occurrences in single patients.

Three patients had apparent hypersensitivity reactions, according to the algorithm described above, which were reported as SAEs:

- A 52 year-old female patient in the PBO QW + 26-week GC taper group experienced Grade 3 paraesthesia on Study Day 24. Prior to the paraesthesia, the most recent dose of blinded study treatment was on Study Day 22. Up to this date, the patient had received 4 blinded SC injections and was receiving open-label GC. The event was considered serious due to patient hospitalisation and was considered related to GC treatment by the investigator. Study treatment was continued and the event resolved after 342 days.

- A 74 year-old female patient in the PBO QW + 52-week GC taper group was diagnosed with Grade 3 herpes zoster on Study Day 185. The patient received treatment for the event which was reported as a serious AE due to patient hospitalization and was considered related to both blinded TCZ and blinded GC treatment by the investigator. Study treatment was interrupted and the event resolved after 56 days.

- A 73 year-old female patient in the TCZ Q2W + 26-week GC taper group experienced Grade 3 hypersensitivity on Study Day 141. Prior to the event, the most recent dose of blinded study treatment was on Study Day 141. Up to this date, the patient had received 11 blinded SC injections and was receiving blinded GC according to the tapering schedule. The event was reported as serious due to hospitalization of the patient and was considered related to blinded TCZ study treatment by the investigator. The patient was withdrawn from blinded TCZ study treatment and the event resolved after 2 days.

Of the three patients with apparent hypersensitivity reactions, from a clinical perspective only one case was consistent with hypersensitivity.

Two patients, both in the TCZ Q2W + 26-week GC taper group had clinically significant hypersensitivity reactions (i.e. hypersensitivity reactions leading to withdrawal from study treatment). No other patients in any treatment group experienced a clinically significant hypersensitivity reaction. As noted above, a conservative approach was taken to identify

potential hypersensitivity reactions, and this analysis included all AEs, regardless of whether or not they were clinically consistent with hypersensitivity.

- A 67 year-old female patient experienced Grade 3 rash with onset on Study Day 7 (within 24 hours after receiving the second blinded SC injection). The event was considered by the investigator to be related to blinded TCZ treatment, which was discontinued. The patient received treatment for the rash (fexofenadine) and the event improved. The status of the rash was unknown at the time of the data cut-off for the 52-week analysis.

- A73 year-old female patient experienced Grade 3 hypersensitivity on Study Day 141 which was reported as an SAE.

Injection-site reactions (ISRs)

AEs (all-grades) occurring at the site of a SC injection were reported in six patients in the TCZ QW + 26-week GC taper group, seven patients in the TCZ Q2W + 26-week GC taper group, five patients in the PBO QW + 26-week GC taper group, and one patient in the PBO QW + 52-week GC taper group (Table 43). The only ISRs reported in more than one patient in any treatment group were injection site pruritus and injection site reaction, each reported in two patients in the TCZ Q2W + 26-week GC taper group.

With the exception of two Grade 2 ISRs (injection site pain, erythema) all other ISRs were Grade 1 in severity and no ISR was reported as a serious AE or required patient withdrawal from treatment.

Table 23: Adverse events of special interest in Phase III GiACTA

Adverse Events of Special Interest:	PBO QW +-week GC taper (n=50)	PBO QW +52-week GC taper (n=51)	TCZ+26-week GC taper (n=100)	TCZ Q2W+ 26-week GC taper (n=49)
Infections and infestations	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
Serious infections	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Opportunistic infections	0	2 (3.9%)	0	1 (2.0%)
Malignancy AEs	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Malignancy AEs (excluding NMSC)	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Serious Hepatic AEs	0	0	0	0
Serious Stroke	0	1 (2.0%)	0	1 (2.0%)
Serious myocardial infarction	0	0	0	0
Anaphylactic reaction AEs (SMQN)	0	0	0	0
Anaphylactic Reaction AEs (Sampson's criteria)	0	0	0	1 (2.0%)*
Serious gastrointestinal perforation AEs	0	0	0	0
Gastrointestinal perforation AE Confirmed by Medical Review	0	0	0	0
Serious bleeding AEs	0	0	0	0
Serious demyelinating AEs	0	0	0	0

(Hoffman-La Roche Ltd. 2016)

B.2.10.3 Exposure to treatment

Exposure to tocilizumab

Compliance to treatment was high with median dose intensity of 100% (range of means 97.9%–98.7%) across the treatment groups. The majority of patients in the TCZ QW + 26-week GC taper group (82%), TCZ Q2W + 26-week GC taper group (84%), PBO+26-week group (86%) and PBO+52-week group (80%) missed no more than one dose of blinded SC treatment during the 52 weeks of the study. Dose modifications were infrequent: the most common reason for non-compliance with study medication was that less than the full amount of the pre-filled syringe was administered. (Hoffman-La Roche Ltd. 2016)

Table 24: Exposure to blinded SC study treatment

	PBO QW + 26-week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Treatment duration (days)				
Mean (SD)	324.0 (79.4)	331.6 (83.4)	317.2 (96.7)	324.3 (82.0)
Median	358.0	358.0	358.0	358.0
Range	44 - 368	43 - 369	9 - 365	6 - 371
Number of doses				
Mean (SD)	46.3 (11.1)	47.1 (11.7)	45.1 (13.7)	46.5 (11.6)
Median	52.0	51.0	51.5	52.0
Range	7 - 53	7 - 53	2 - 53	2 - 53
Total cumulative dose (mg)				
Mean (SD)	0.0 (0.0)	0.0 (0.0)	7304.6 (2215.4)	3785.5 (941.0)
Median	0.0	0.0	8343.0	4212.0
Range	0 - 0	0 - 0	324 - 8586	162 - 4374
Missed doses				
0	37 (74.0%)	29 (56.9%)	58 (58.0%)	36 (73.5%)
1	6 (12.0%)	12 (23.5%)	24 (24.0%)	5 (10.2%)
2	1 (2.0%)	0	6 (6.0%)	4 (8.2%)
3	1 (2.0%)	4 (7.8%)	3 (3.0%)	2 (4.1%)
4	3 (6.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
≥5	2 (4.0%)	2 (3.9%)	5 (5.0%)	1 (2.0%)

(Hoffman-La Roche Ltd. 2016)

As cumulative glucocorticoid dose was a secondary efficacy endpoint in GiACTA, information detailing exposure to GC in GiACTA is given in section B.2.6 Clinical effectiveness results of the relevant trials.

B.2.10.4 Concomitant medications for GCA

Concomitant treatments for GCA (other than blinded study treatment) as determined by the investigator were reported for 67% of patients in the TCZ QW and TCZ Q2W + 26-week GC taper groups, 78% of patients in the PBO QW + 26-week GC taper group and 71% of patients in the PBO QW + 52-week GC taper group. (Hoffman-La Roche Ltd. 2016)

Antimetabolites (methotrexate), salicylates (aspirin) analgesics (mainly paracetamol) and non-steroidal anti-inflammatory drugs were among the most commonly reported concomitant

treatments for GCA. (See Table 25 for summary; concomitant treatments for GCA taken by ≤2 patients in any treatment group are not summarised.) (Hoffman-La Roche Ltd. 2016)

Steroids (including low-dose glucocorticoid treatment) were the most commonly reported concomitant treatments for GCA. The use of steroids in addition to the protocol defined prednisone taper may appear high. These numbers must be interpreted in the context that they include also concomitant glucocorticoid medications which were stopped on Study Day 1 (prior to initiation of study medication) as well as concomitant medications for GCA in patients withdrawn from study treatment but who were being treated in safety follow-up. (Hoffman-La Roche Ltd. 2016)

Table 25: Concomitant medications (treatments for GCA) in the GiACTA trial (ITT Population)

	PBO QW + 26-week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Steroids				
Total number of pts with ≥1 treatment	30 (60.0%)	25 (49.0%)	52 (52.0%)	23 (46.9%)
Total number of treatments	36	35	82	41
Salicylates				
Total number of pts with ≥1 treatment	9 (18.0%)	8 (15.7%)	18 (18.0%)	9 (18.4%)
Total number of treatments	9	8	18	9
Antimetabolites				
Total number of pts with ≥1 treatment	8 (16.0%)	9 (17.6%)	11 (11.0%)	5 (10.2%)
Total number of treatments	12	15	15	7
Analgesics				
Total number of pts with ≥1 treatment	8 (16.0%)	6 (11.8%)	3 (3.0%)	7 (14.3%)
Total number of treatments	15	7	3	11
Non-steroidal anti-inflammatories				
Total number of pts with ≥1 treatment	2 (4.0%)	3 (5.9%)	5 (5.0%)	1 (2.0%)
Total number of treatments	2	3	10	1

(Hoffman-La Roche Ltd. 2016)

B.2.10.5 GC-related adverse events

GC-related adverse events were pre-specified to be summarised in the clinical study report.

The percentage of patients reporting an AE considered related to glucocorticoid use by the investigator was 50% (50/100) of patients in the TCZ QW + 26-week GC taper group, 61% (30/49) of patients in the TCZ Q2W + 26-week GC taper group, 62% (31/50) of patients in the PBO QW + 26-week GC taper group and 49% (25/51) of patients in the PBO QW + 52-week GC taper group. (Hoffman-La Roche Ltd. 2016)

The SOCs with the highest incidence of AEs considered related to study treatment by the investigator were Infections and Infestations (most commonly nasopharyngitis, bronchitis and upper respiratory tract infection), Skin and Subcutaneous Tissue Disorders (most commonly alopecia), Psychiatric Disorders (most commonly anxiety and insomnia), and General Disorders and Administration Site Conditions (most commonly oedema peripheral).

Table 26: Summary of adverse events related to glucocorticoid study drug, by system organ class (Safety Population)

n (%)	PBO QW + 26-week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Infections and infestations				
Number of patients with ≥1 AE	10 (20.0%)	11 (21.6%)	24 (24.0%)	16 (32.7%)
Total number of events	18	33	41	16
Skin and subcutaneous disorders				
Number of patients with ≥1 AE	4 (8.0%)	7 (13.7%)	7 (7.0%)	7 (14.3%)
Total number of events	4	9	7	7
Psychiatric disorders				
Number of patients with ≥1 AE	7 (14.0%)	5 (9.8%)	6 (6.0%)	4 (8.2%)
Total number of events	9	6	7	4
General disorders and administration site conditions				
Number of patients with ≥1 AE	5 (10.0%)	2 (3.9%)	9 (9.0%)	4 (8.2%)
Total number of events	5	2	11	5
Eye disorders				
Number of patients with ≥1 AE	6 (12.0%)	5 (9.8%)	5 (5.0%)	2 (4.1%)
Total number of events	9	7	6	2
Musculoskeletal and connective tissue disorders				
Number of patients with ≥1 AE	3 (6.0%)	2 (3.9%)	6 (6.0%)	6 (12.2%)
Total number of events	5	4	7	7
Gastrointestinal disorders				
Number of patients with ≥1 AE	6 (12.0%)	4 (7.8%)	1 (1.0%)	3 (6.1%)
Total number of events	7	5	3	3

Nervous system disorders				
Number of patients with ≥1 AE	6 (12.0%)	4 (7.8%)	2 (2.0%)	2 (4.1%)
Total number of events	8	6	2	2
Vascular disorders				
Number of patients with ≥1 AE	2 (4.0%)	3 (5.9%)	4 (4.0%)	4 (8.2%)
Total number of events	2	3	4	5
Metabolism and nutrition disorders				
Number of patients with ≥1 AE	3 (6.0%)	2 (3.9%)	2 (2.0%)	2 (4.1%)
Total number of events	4	4	2	2
Respiratory, thoracic and mediastinal disorders				
Number of patients with ≥1 AE	3 (6.0%)	4 (7.8%)	1 (1.0%)	0
Total number of events	4	6	1	0
Investigations				
Number of patients with ≥1 AE	2 (4.0%)	0	4 (4.0%)	1 (2.0%)
Total number of events	2	0	4	1
Cardiac disorders				
Number of patients with ≥1 AE	1 (2.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
Total number of events	1	2	2	1
Injury, poisoning and procedural complications				
Number of patients with ≥1 AE	0	2 (3.9%)	4 (4.0%)	0
Total number of events	0	2	4	0
Blood and lymphatic system disorders				
Number of patients with ≥1 AE	2 (4.0%)	0	2 (2.0%)	0
Total number of events	3	0	2	0
Endocrine disorders				
Number of patients with ≥1 AE	0	2 (3.9%)	2 (2.0%)	0
Total number of events	0	2	2	0
Renal and urinary disorders				
Number of patients with ≥1 AE	0	0	2 (2.0%)	0
Total number of events	0	0	3	0
Reproductive system and breast disorders				
Number of patients with ≥1 AE	0	0	1 (1.0)%	1 (2.0)%
Total number of events	0	0	1	1
Ear and labyrinth disorders				
Number of patients with ≥1 AE	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
Immune system disorders				
Number of patients with ≥1 AE	1 (2.0%)	0	0	0

Total number of events	1	0	0	0

(Hoffman-La Roche Ltd. 2016)

Retrospective analysis

In addition to having a prespecified summary of GC-related AEs, events that were consistent with glucocorticoid-induced toxicity from GiACTA were analysed retrospectively using criteria that were developed by Roche prior to GiACTA database lock.

The publication by Miloslavsky et al. defines the glucocorticoid-toxicity index as an instrument for the assessment of glucocorticoid-related morbidity, optimally used in prospective randomized controlled clinical trials involving glucocorticoids. (Miloslavsky et al. 2017) Roche adapted the medical concepts from the publication into MedDRA preferred terms to create a glossary for extracting glucocorticoid-induced toxicity events from GiACTA (see Table 27). The events included in the publication or the glossary are not unique to glucocorticoids, and may also be attributable to the other medications used in the trials, including study medications. Neither the publication nor the analysis presented here takes causality into consideration.

Table 27: Glossary of Glucocorticoid-Induced Toxicity Events: Preferred Term

Hypertensive crisis	Cataract subcapsular	Peptic ulcer
Hypertensive emergency	Chorioretinopathy	Peptic ulcer haemorrhage
Malignant hypertension	Intraocular pressure increased	Peptic ulcer perforation
Adrenal insufficiency	Glucose tolerance decreased	Peptic ulcer perforation obstructive
Adrenocortical insufficiency acute	Glucose tolerance impaired	Peptic ulcer obstructive
Secondary adrenocortical insufficiency	Hyperglycaemia	Acne
Adrenal suppression	Diabetes mellitus	Dermatitis acneiform
Osteonecrosis Fracture	Diabetic nephropathy	Increased tendency to bruise
Stress fracture	Diabetic neuropathy	Hirsutism
Cervical vertebral fracture	Diabetic retinopathy	Skin atrophy
Thoracic vertebral fracture	Diabetic autonomic neuropathy	Skin striae
Lumbar vertebral fracture	Diabetic blindness	Skin erosion
Hip fracture	Diabetic coma	Skin ulcer
Bone density decreased	Diabetic complication	Psychosis
Osteopenia	Diabetic eye disease	Hallucination
Osteoporosis	Diabetic hyperglycaemic	Delusion

	coma	
Tendon rupture	Diabetic hyperosmolar coma	Insomnia
Metabolic myopathy	Diabetic metabolic decompensation	Mania
Myopathy	Diabetic mononeuropathy	Cognitive disorder
Myopathy toxic	Diabetic retinal oedema	Depression
Cataract		Substance-induced psychotic disorder

In GiACTA, during the 52-week double-blind phase (Part 1), the proportion of patients who experienced any potentially glucocorticoid-induced toxicity events was numerically lower in both the TCZ groups (21.0% in TCZ QW and 18.4% in TCZ Q2W + 26-week GC taper group) compared with the placebo groups (28.0% in PBO QW + 26 week and 29.4% in PBO QW + 52 week GC taper). See Table 26 for details of details of events per system organ class.

These data were analysed retrospectively and were not based on standard or pre-specified criteria. Additionally, the duration of the study was considered too short for some of these events to manifest.

Table 28: Summary of AEs commonly associated with GC use (retrospective analysis in safety population)

	PBO QW + 26-week GC Taper n = 50	PBO QW + 52-week GC Taper n = 51	TCZ QW + 26-week GC Taper n = 100	TCZ Q2W + 26-week GC Taper n = 49
Total no. pts with ≥1 AE	14 (28.0%)	15 (29.4%)	21 (21.0%)	9 (18.4%)
Total number of events	17	19	28	9
Psychiatric disorders				
Total no. pts with ≥1 AE	6 (12.0%)	5 (9.8%)	6 (6.0%)	3 (6.1%
Total number of events	7	5	7	3
Eye disorders				
Total no. pts with ≥1 AE	3 (6.0%)	5 (9.8%)	5 (5.0%)	1 (2.0%)
Total number of events	3	7	5	1
Musculoskeletal and connective tissue disorders				
Total no. pts with ≥1 AE	2 (4.0%)	2 (3.9%)	4 4.0%)	3 (6.1%)
Total number of events	2	2	4	3
Investigations				
Total no. pts with ≥1 AE	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
Total number of events	2	2	2	1
Metabolism and nutrition disorders				
Total no. pts with ≥1 AE	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
Total number of events	2	0	2	1
Injury, poisoning and procedural complications				
Total no. pts with ≥1 AE	0	1 (2.0%)	3 (3.0%)	0
Total number of events	0	1	3	0
Skin and subcutaneous tissue disorders				
Total no. pts with ≥1 AE	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
Total number of events	1	1	2	0
Vascular disorders				
Total no. pts with ≥1 AE	0	1 (2.0%)	2 (2.0%)	0
Total number of events	0	1	2	0
Endocrine disorders				
Total no. pts with ≥1 AE	0	0	1 (1.0%)	0
Total number of events	0	0	1	0

B.2.10.6 Safety from GiACTA Part 2 − Open-Label Extension

After the 52-week double-blind treatment period, all patients entered the 104-week long-term follow-up (Part 2) of the study. Based on the investigator's assessment of GCA disease activity at the end of the 52-week double-blind period, the patient was either given the option to receive open-label TCZ 162 mg QW (in case of persistent disease activity/flare) or was followed up off treatment for maintenance of established remission at the investigators discretion. Remission at Week 52 constituted response to either TCZ/placebo treatment or escape treatment with prednisone in Part 1. A patient's GCA therapy could be adjusted at any time during Part 2 of the study at the investigator's discretion and on the basis of disease activity. This could have included initiation/termination of open-label TCZ 162 mg QW and/or changes to corticosteroid or methotrexate (MTX) treatment. The objective of Part 2 of the study was to assess the long-term safety and maintenance of efficacy after 52 weeks of therapy with TCZ, to explore the rate of relapse and the requirement for TCZ therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of TCZ.

A total of [redacted] of the [redacted] reported [redacted] in Part 2 of GiACTA (Table 29). The [redacted], with [redacted] and [redacted]. [redacted] occurred in a patient who was [redacted], and the remaining [redacted] occurred in patients who were in the [redacted]. [redacted] events of [redacted], were reported. [redacted] event of [redacted] was reported in a patient who was [redacted] was reported in a patient who was [redacted] Hypersensitivity reactions during Part 2 were not evaluated. There were no AESIs reported for gastrointestinal perforation, serious/medically significant bleeding, or hepatic events.

Table 29: Individual patient summary of AESI in Part 2 (Open-label extension) of GiaCTA

Treatment Group (Part 1)	Subtype	AESI	Onset Day	On open label TCZ at time of event	TCZ exposed
PBO QW + 26-wk GC taper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO QW + 52 wk GC taper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ QW + 26 wk GC taper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	
TCZ Q2W + 26 wk GC taper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.2.10.7 Conclusions

The extent of exposure to tocilizumab / placebo was well balanced across all four treatment groups, with a mean duration in the study of at least 0.929 years and with patients receiving double-blind tocilizumab / placebo for most of their duration in the study.

Treatment with tocilizumab was well-tolerated in the 52-week double-blind phase (Part 1) of GiACTA; the incidence of SAEs and withdrawal due to AEs was low, no deaths were reported, and no new safety signals related to tocilizumab treatment were observed. The nature of AEs and AESIs observed in the tocilizumab groups was similar to that in the placebo group, and the overall rates of AEs in the tocilizumab groups were numerically lower compared with the placebo groups. The proportions of patients who experienced any AE or a SAE were very similar in the TCZ QW and TCZ Q2W + 26-week GC taper groups.

Overall, the safety profile of SC tocilizumab in patients with GCA observed in Phase III GiACTA is generally consistent with that reported in the Phase II NCT01450137 investigator-

initiated study in GCA with IV tocilizumab and with the established, well characterised safety profile of IV tocilizumab in rheumatoid arthritis.

There was a higher proportion of patients with SAEs in the control groups treated with GCs alone, which may be related to the significantly higher cumulative GC exposure in these patients and suggestive of a role of GC-related toxicity in this respect.

B.2.11 On-going studies

The Phase III GiACTA study is subject to an on-going open-label 104-week extension; last patient last visit will be in April 2018 and data will be published thereafter.

B.2.12 Innovation

Glucocorticoids (GC) are the mainstay of treatment for GCA and although they are highly effective at inducing remission of systemic inflammation and preventing acute damage (e.g. vision loss), this comes with a high toxicity burden, with approximately 80% of patients suffering GC-related AEs at 10-year follow-up. (Proven et al. 2003) In addition, GCs are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare of symptoms during reduction or discontinuation of GCs. (Proven et al. 2003) Other agents, including azathioprine, cyclophosphamide, methotrexate (MTX), infliximab, and etanercept, have shown conflicting or no evidence of benefit in the treatment of GCA. An effective and safe glucocorticoid-sparing therapy for patients with new-onset or relapsing GCA remains elusive and constitutes a high unmet medical need.

Data to support the efficacy of tocilizumab in adult patients with giant cell arteritis are provided from a pivotal Phase III trial (GiACTA) and a supporting Phase II NCT01450137 investigator-initiated study, which have been discussed within this application.

There are benefits of tocilizumab for the treatment of GCA not captured in the EQ-5D, as shown in the quality of life benefits reported in SF-36 and the Patients' Global Assessment taken with the visual analogue scale (see section B.2.6.5 Health related quality of life).

Roche believes that the results of the GiACTA trial mark the beginning of a breakthrough in the treatment of GCA by providing unequivocal evidence of not only compelling and clinically meaningful sustained disease control elicited by tocilizumab, but also by showing it is able to

do so long after glucocorticoid therapy has been discontinued. GiACTA is the largest clinical trial ever conducted in GCA, with a rigorous design applying a stringent and clinically meaningful endpoint of continuous remission for 40 weeks and discontinuation of glucocorticoids for 6 months. Tocilizumab represents a step change in the management of the disease.

The primary results demonstrate a compelling and superior treatment benefit of tocilizumab combined with a 26-week glucocorticoid regimen in comparison to both a short 26-week schedule and a longer 52-week schedule which more closely matches UK clinical practice. The treatment effect is borne out across all indices of efficacy and subgroup analyses. Moreover, a significant glucocorticoid sparing effect of tocilizumab was shown which, together with the treatment benefit described above, serves to address the two areas of unmet need: maintenance of long-term disease control after the discontinuation of high-dose GCs as well reduction of GC-related AEs.

In light of this, Promising Innovative Medicine (PIM) designation for tocilizumab in GCA was issued by the MHRA on 25th May 2017. (Since regulatory timelines were brought forward, there was no time to implement Early Access to Medicines Scheme [EAMS].)

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal (interim) findings from the clinical evidence

In summary, the findings of the Phase III GiACTA clinical trial were:

- Tocilizumab + 26-week glucocorticoid regimen induced and more effectively sustained remission at 1 year compared with a 26-week (primary endpoint) or a 52-week (key secondary endpoint) regimen of glucocorticoids given alone in patients with newly diagnosed and relapsing GCA (both $p<0.0001$)

- Tocilizumab significantly increased the time to flare compared with placebo + 26-week GC group ($p<0.0001$ for both doses)

- Tocilizumab improved HRQoL from baseline and compared with placebo + GC on generic instruments measuring overall HRQoL and fatigue (although for some measures the predefined statistical significance was not achieved)

- No new safety signals were observed for tocilizumab and were similar to age-matched rheumatoid arthritis patients
- The nature of AEs observed in the tocilizumab groups was similar to that in the placebo group, and the overall rates of AEs in the tocilizumab groups were numerically lower compared with the placebo groups

These data are reinforced by the Phase II NCT01450137 trial with IV tocilizumab (see Appendix K for details):

- IV tocilizumab effectively induces and maintains remission of GCA after 12 weeks and following a prednisolone taper to a dose of 0.1 mg/kg per day
- This treatment effect is maintained out to Week 52
- The proportions of patients with SAEs were similar in the tocilizumab and placebo groups

The principal findings from Part 1 of the GiACTA trial are supported by the unpublished data from Part 2 of the study (Roche Products Ltd. 2017):

- Of the 35 patients that met the primary endpoint following treatment with tocilizumab in Part 1 of the study, 46% flared during Part 2 suggesting that treatment with tocilizumab is required beyond 1 year

[redacted]

  - Higher proportions of patients treated with TCZ Q2W during Part 1 of the study flared after discontinuation of treatment at Week 52 compared to those treated with TCZ QW during Part 1 of the study, suggesting the QW dose provides more effective maintenance of disease control following one year of treatment

[redacted]

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

There were a number of challenges in designing the GiACTA study:

First, no validated outcome measures are available to assess GCA in clinical trials. To address this, stringent definitions of flare and remission were used. Furthermore, the requirement for escape therapy with GC was part of the definition of flare. This strategy ensured that symptoms were sufficiently severe to justify an increase in the GC dose and created consistency in instituting changes in medications across trial sites.

Secondly, tocilizumab lowers serum CRP concentrations, which poses a risk of unblinding. Consequently, all the investigators and patients were not aware of the CRP concentrations. To address safety concerns, a dual-assessor approach was used in which the laboratory assessor was required to notify the efficacy assessor of clinically significant elevations in the ESR. Only seven flares (all in the placebo groups) were associated with elevations in the ESR without signs or symptoms of GCA. The exclusion of these flares from the analyses did not alter the trial conclusions.

Blinded steroid taper

To our knowledge, this is the first clinical trial to use blinded, variable-dose, variable-duration GCs. This approach permitted the overcoming of significant technical and operational challenges to fulfil the requirements of a complex clinical trial protocol. This was necessary to ensure an unbiased evaluation of the ability of tocilizumab to act as a steroid-sparing treatment in GCA.

A 2-year, open-label, follow-up phase of this trial will provide additional information pertaining to the safety and efficacy of tocilizumab beyond 52 weeks.

The demographics of the Phase III GiACTA population reflect the epidemiologic profile of GCA in the UK (Petri et al. 2015) and the study was generally reflective of UK practice for diagnosis of GCA, with the control arm mirroring current standard of care. There were however some differences:

- many patients were enrolled based on large-vessel imaging rather than TAB, reflecting the increased use of imaging to diagnose large-vessel vasculitis since development of the 1990 ACR criteria for GCA
- Revised ACR 1990 diagnostic criteria were used to enrol patients, allowing the consideration of a broader array of cranial symptoms that occur in GCA beyond

headache alone (e.g. jaw claudication, scalp tenderness, ischaemia-related vision loss), PMR symptoms related to GCA proven by biopsy or imaging and evidence of large vessel vasculitis seen in imaging

These two changes are reflective of the some of the latest thinking on improvements in diagnosis. (Luqmani et al. 2016)

The GC taper of 26 weeks in the GiACTA tocilizumab arms is relatively rapid and shorter than that currently recommended by BSR Guidelines. However, to better reflect UK Practice of a slower taper, a 52-week GC taper arm was also added in to one of the control arms and data analysed against this longer taper as a secondary endpoint.

The primary results reported in this application demonstrate a compelling and superior treatment benefit of tocilizumab combined with a 26-week glucocorticoid regimen in comparison to both a short 26 weeks schedule and a longer 52 weeks schedule more in keeping with current standard of care. The treatment effect is borne out across all indices of efficacy and subgroup analyses. Moreover, a significant glucocorticoid sparing effect of tocilizumab was shown which, together with the treatment benefit described above, serves to address the two areas of unmet need -maintenance of long-term disease control after the discontinuation of high-dose glucocorticoids as well reduction of GC-related AEs.

The study results revealed no new safety signals related to tocilizumab treatment. The safety profiles were balanced across the tocilizumab- and placebo-treated groups, in agreement with the well characterized safety profile of tocilizumab in other indications.

There was a higher proportion of patients with SAEs in the control groups treated with glucocorticoids alone, which may be related to the significantly higher cumulative glucocorticoid exposure in these patients and suggestive of a role of glucocorticoid-related toxicity in this respect.

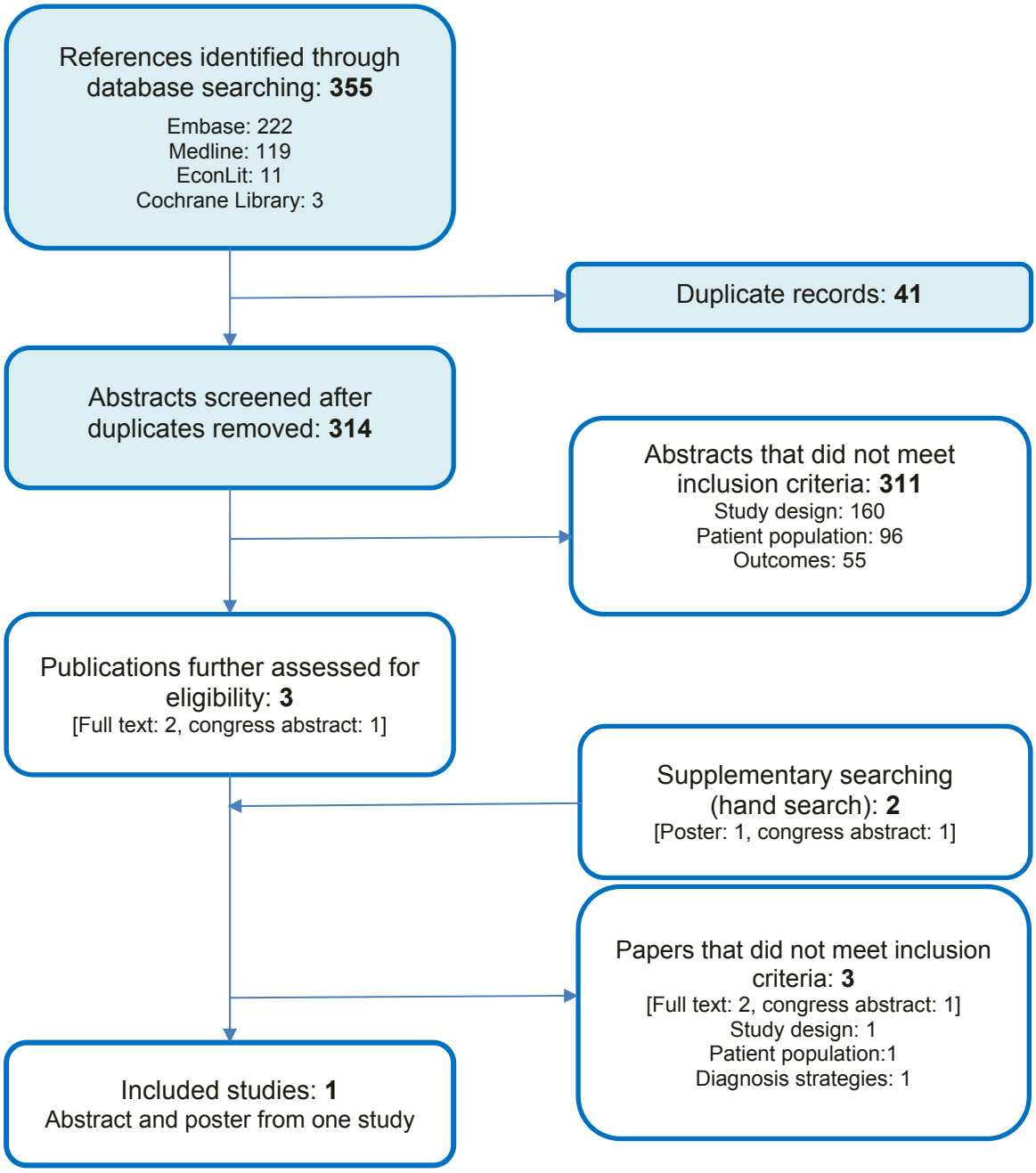
B.3. Cost effectiveness

B.3.1 Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See section 3.1 of the user guide for full details of the information required in appendix G.

A comprehensive a systematic literature review (SLR) of economic evaluations was performed (see Appendix G for details) and a single cost-effectiveness study was identified as being relevant to the decision problem. (Orfanos 2017) Briefly, searches were based on the filters provided by the Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Guidelines Network (SIGN) 2017) and the InterTASC Information Specialists' Sub-Group (ISSG) (The InterTASC Information Specialists' Sub-Group (ISSG) 2017) Searches were run on 08 May 2017 and screening was performed according to the usual double-blind method. Figure 8 presents the PRISMA flow diagram, showing the attrition rate at each stage of the review.

Figure 8: PRISMA flow diagram of included economic evaluations



The identified economic evaluation, discussed in further detail in Appendix G, has been summarised below in Table 30. A congress poster and abstract presented the *de novo* model summarised in B.3.2 Economic analysis, which is the basis of the model used in this submission. This poster and this dossier are based on the same economic model; however, the incremental cost-effectiveness ratio (ICER) values reported in the poster differ to this dossier, due to the inclusion of aspects more relevant to the UK (for example, data from the UK Clinical Practice Research Datalink [CPRD] for GC-related AEs in people with GCA).

Table 30: Study details of included economic evaluation

Author, year	Country where study was performed	Study population	Model characteristics/ Type of evaluation	Intervention	Comparator	Time horizon	Outcomes	Sensitivity analysis	Total cost (for each intervention)	Incremental outcome ratio
Orfanos, 2017 (Orfanos 2017)	UK	Patients with GCA	Cost-effectiveness analysis (semi-Markov model)	TCZ QW + 26-week GC taper or TCZ Q2W + 26-week GC taper	GC alone in 52-week tapering (PBO QW + 52-week GC taper)	Lifetime	Simulated adverse events (disease flares, vision loss, stroke, related fractures and diabetes) Total, disaggregated and incremental costs Utilities Cost-effectiveness referenced but not reported	NR	TCZ QW: £2,457.57 TCZ Q2W: £2,732.37 PBO 52: £5,987.52	TCZ QW vs PBO 52: £3,529.95 TCZ Q2W vs PBO 52: £3,255.15

Abbreviations: GCA: Giant Cell Arteritis; PBO: placebo; QW: weekly dosing; Q2W: biweekly dosing; NR: not reported; TCZ: tocilizumab; UK: United Kingdom

B.3.2 Economic analysis

Roche built a *de novo* model for this NICE appraisal as there were no cost-effectiveness models previously published, for either tocilizumab or previous NICE appraisals within GCA. The only previously published economic analysis within GCA was published by the School of Health and Related Research (ScHARR) to review the cost-effectiveness of different diagnostic techniques for GCA. (Luqmani et al. 2016)

The only cost-effectiveness model identified from the comprehensive systematic literature review was a poster publication of the *de novo* model used in this appraisal. B.3.1 Published cost-effectiveness studies; see also Appendix G.

B.3.2.1 Patient population

Whilst the GiACTA trial consisted of four treatment arms, only two are used in the model: the TCZ QW + 26-week GC taper group and the PBO QW + 52-week GC taper group.

- The TCZ Q2W + 26-week GC taper group was excluded from the model as it is not stated posology section of the SmPC
- The PBO QW + 26 week GC taper group was excluded from the model, as the 52-week GC taper regimen better reflects clinical practice in the UK

The cost-effectiveness model includes the full ITT population of these two groups in the GiACTA trial (B.2.6 Clinical effectiveness results of the relevant trials). This population reflects the NICE final scope and decision problem, as well as the CHMP Positive Opinion for Marketing Authorisation. Therefore, the model and the evidence base are directly relevant to the decision problem.

Patients who no longer need to receive treatment, due to having inactive GCA, are accounted for in the model as those patients who have completed their predicted GC tapering. They have achieved maintained remission on 0 mg GC. These patients may experience subsequent relapse/flare in future.

B.3.2.2. Model structure

A *de novo* semi-Markov model was built by Roche to evaluate the costs and benefits of tocilizumab plus GC versus GC alone.

The *de novo* model structure was conceptualised on the basis of the known aetiology of GCA, the GiACTA pivotal trial data, NICE Scientific Advice (April 2012) and the opinion of

practicing UK clinicians and independent UK HTA experts (see section B.1.3.7 External expert input). There are seven health states within the model (Figure 9);

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

People with GCA can enter the model either on relapse/flare or in the remission state, and will initiate treatment with either tocilizumab plus GC or GC alone. Once entering a remission state, patients can remain on remission until their first flare. While on remission, patients follow the GC tapering as defined in the GiACTA protocol: 26 weeks for tocilizumab patients and 52 weeks for GC-only patients.

The first transition to flare state from these remission states is via time-dependent transition probabilities, derived from the Kaplan-Meier curves of time to first flare based on GiACTA trial data (see Appendix E). Extrapolation of these transition probabilities beyond the study follow-up period is via survival curves fit to the GiACTA data.

Following the first flare, the patient will transition back to remission on an ‘escape’ GC regimen; a different transition probability is then applied for subsequent flares. The probability of subsequent flares is modelled separately, based on a Poisson regression, as was reported from the GiACTA trial.

The extrapolation approach differed for the time to first flare and the time to subsequent flare to match in each case the best visual fit for the GiACTA trial data. This is discussed in more detail in section B.3.3 Clinical parameters and variables.

Based upon the GiACTA trial, the probability of re-flaring after an initial flare is higher than the probability of initial flare. Additionally, the GC exposure can differ for relapsed patients compared with patients who do not relapse, meaning that GC-related AEs are expected to be increased.

Cost and quality of life impacts are modelled for each flare based upon data from a large survey of UK clinicians and quality of life data from the GiACTA trial (B.2.6.5 Health related quality of life).

In addition, the model accounts for GCA-related complications and for GC-related AEs. GCA-related complications can only occur from the relapse/flare health state, while steroid-related AEs can occur from any health state in the model, except death.

GCA-related complications and GC-related AE were selected for inclusion in the model based upon the following criteria:

- High impact on either cost to the NHS or patient quality of life
- Availability of evidence to model the rate of the event
- Ability to clearly attribute the AE to either GCA or GC use

The HTA assessment conducted by Luqmani et al was used as a starting point for selection of which events to include, as the evidence for these was taken to be of sufficient quality and robustness for a subsequent NICE HTA appraisal. (Luqmani et al. 2016) The model used within the Luqmani HTA report included the following events:

- Visual complications (GCA related)
- Stroke (GCA related)
- Fractures (GC related)
- Diabetes (GC related)
- Hyperglycaemia (GC related)
- Symptomatic steroid myopathy (GC related)
- Steroid psychosis (GC related)
- Steroid-related lost quality of life (GC related)

Of these, only the first four have been included within this economic model as these were the events with the greatest impact to patient quality of life and cost for evaluation. In addition, GC-related AEs of osteoporosis and infection have also been incorporated, since similarly they represent substantial impact to the patient's quality of life, NHS costs, and can be robustly estimated from the CPRD analysis conducted by Roche alongside this clinical development.

The impact of steroids on a patient's quality of life was also considered (Luqmani et al. 2016), using a disutility value originally published in a decision-analytic model of GCA management (Niederkohr and Levin 2005).

In line with the NICE scope, the impact of GCA-related aortic aneurism was considered for inclusion within the economic model; however, given that Luqmani et al did not include this

due to a lack of evidence, and no alternative source of robust data was identified, this was not included in the model.

In addition to the four adverse events that have been included in the model, it is understood that there are a considerable number of other GC-related AEs - the rates of these events have not been included within this model (and in fact a considerable number also not included within the Luqmani model). This means that the impact of the significant GC-sparing effect of tocilizumab will be underestimated.

The probabilities of developing GC-related AEs are time dependent and linked to the current cumulative dose of GC (in mg) that is recorded in the model for each treatment arm. The probabilities of developing GCA-related AEs are also time dependent and linked to the whether or not the patient is experiencing a relapse/flare – again this is likely an underestimate of the benefits of tocilizumab since GC-related complications can occur outside of the relapse/flare state.

The event rates for GCA-related complications and GC-related AEs are derived from analysis of real world data comparing cumulative steroid burden in GCA patients and the rate of fracture and diabetes. (Wilson et al. 2017g) The cumulative GC burden for people with GCA is also linked to the CPRD report, to ensure relevance to UK clinical practice.

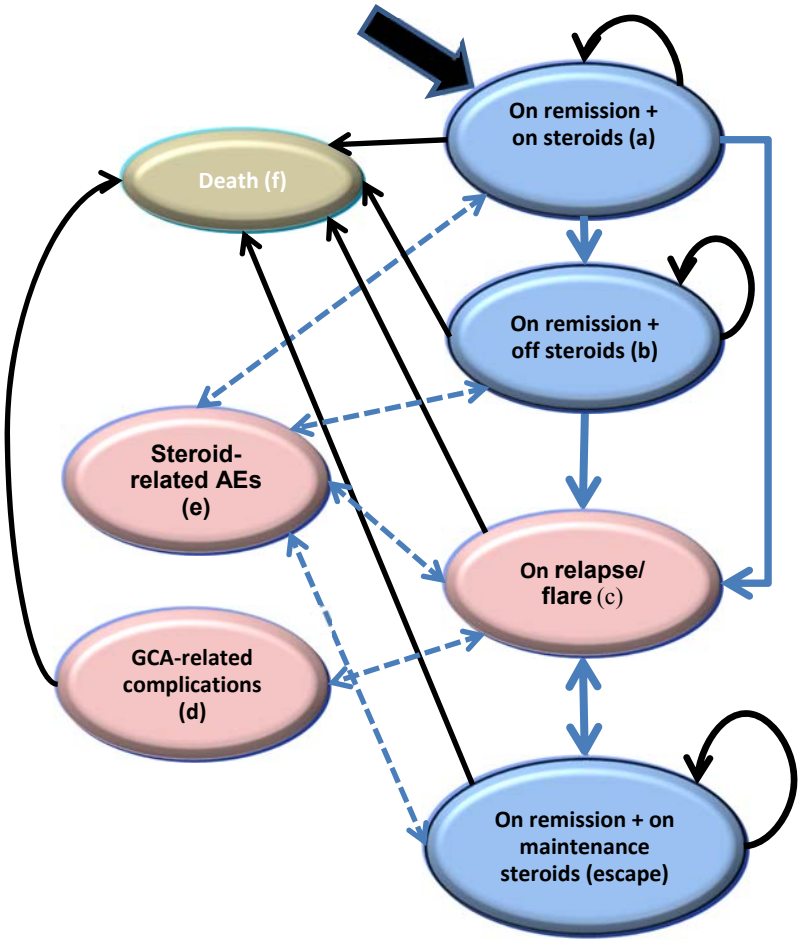
For patients that develop AEs, relevant costs are applied in the model. Quality of life decrements are also applied for GCA-related AEs but not for GC-related AEs, for the purpose of avoiding double counting of disutility. (Ara and Wailoo 2012)

Death is the absorbing health state of the model, and patients can die from any other health state. The model accounts for background mortality (based on national lifetables (Office of National Statistics 2016)) but not directly for GCA-related mortality. GCA-related mortality is not modelled since no deaths occurred during the GiACTA trial follow-up; additionally, a recently published systematic literature review and meta-analysis from Hill et al indicates no overall increase in long-term mortality for GCA patients. (Hill et al. 2017) However, the model adjusts background mortality based on the mortality risk due to stroke, which is one of the two common causes of GCA-related mortality, so some GCA mortality is taken into account indirectly.(Wilson et al. 2017a) It is worth noting that the true rate of mortality due to GCA may be underestimated in the model, since aortic aneurisms were not accounted for, and the increased mortality from a hospital setting reported in the same SLR has not been incorporated (mortality rate = 1.61; 95% CI:1.19–2.19) (Hill et al. 2017). Furthermore, when considering the rate of mortality in GCA patients, shortly after diagnosis there was a

significant increase in vascular disorder-related death compared to the expected mortality rate: 62 vs 43, p<0.05. (Nordborg and Bengtsson 1989)

In addition, the CPRD analysis performed by Roche alongside this clinical development demonstrated a significant increase in mortality related to cumulative GC dose in GCA patients compared to matched controls. (Wilson et al. 2017g)

Figure 9: *De novo*, semi-Markov model for evaluating tocilizumab cost-effectiveness for treating GCA



a. 26 weeks for patients receiving tocilizumab and prednisone and 52 weeks for patients receiving prednisone alone.
b. Patients who have not yet flared after the end of tapering.
c. Transition probabilities derived from the Kaplan–Meier curves of time to first flare from the GiACTA trial
d. Stroke and vision loss
e. Fractures and diabetes.
f. Background mortality and GCA mortality taken into account.

Table 31: Features of the economic analysis

Factor	Current appraisal	
	Chosen values	Justification
Time horizon	Lifetime, here equating to 30 years, since the mean patient age at baseline in the GiACTA trial was 69.5 years	NICE reference case
Treatment waning effect	Tocilizumab benefits continued over a lifetime	Early results from OLE suggest that very few patients re-flare after treatment with tocilizumab (B.2.6.6 Longer term disease control)
Discount for utilities and costs	3.5%	NICE reference case
Cycle length	7 days	In line with dosing schedule
Half cycle correction	None	7 day cycle length is sufficiently short
Source of utilities	Health-state utilities from the GiACTA trial and subsequent data analysis, plus GCA-relevant published literature (Niederkohr and Levin 2005) AE-related disutilities from a previous NICE GCA HTA (Luqmani et al. 2016)	NICE reference case
Source of costs	Drug costs are taken from the Dictionary of Medicine and Devices NHS unit costs have been sourced from PSSRU 2016 (Curtis 2016) and Reference Cost Collection for 2015.(Department of Health 2016) GCA related complication costs and GC-related AE costs are taken from relevant literature, including a previous NICE GCA (Kanis et al. 2007; Manson et al. 2009; Luqmani et al. 2016); (National Collaborating Centre for Acute Care 2009; Schmidt et al. 2016) Management costs are taken from third-party market research (Research Partnerships 2017) and the PSSRU 2016 (Curtis 2016)	NICE reference case

This is a *de novo* cost-effectiveness model; therefore, it is not possible to compare with previous NICE appraisals

B.3.2.3 Intervention technology and comparators

Treatments included within the economic model

At the time of submitting to NICE, the Marketing Authorisation for RoActemra® to treat GCA was not published on the Electronic Medicines Compendium, although the CHMP Positive Opinion has been granted. The cost-effectiveness of tocilizumab has been modelled in line with the wording of the CHMP Positive Opinion for Marketing Authorisation.

The comparator treatment, prednisone, is not licensed for the treatment of GCA, but has been modelled according to the GiACTA trial, which in turn reflects the BSR/BHPR Guidelines. (Dasgupta et al. 2010) The BSR/BHPR guidelines also state that steroid-sparing agents can be combined with GCs to reduce the cumulative steroid burden, including immunosuppressants such as methotrexate. Use of immunosuppressants was allowed within the GiACTA trial in line with this guidance although the dose had to remain stable within the double-blind period of the clinical trial.

Duration of treatment

The modelling of tocilizumab + GC versus GC alone reflects the final scope and decision problem, which states the comparator should be 'established treatments. The 52-week GC tapering regimen in the GiACTA trial reflects the most rapid taper regimen from the BSR guidelines with no relapse/flare event. Clinicians often use a longer tapering regimen described in the scope as 18-24 months – summarised in section B.1.3 Health condition and position of the technology in the treatment pathway Therefore, the cumulative steroid burden for people with GCA will often be greater in clinical practice than that seen in the GiACTA trial. (Wilson et al. 2017g)

The CHMP Positive Opinion for Marketing Authorisation states tocilizumab can be given beyond 52 weeks depending on disease activity, physician discretion, and patient choice – see B.1.3 Health condition and position of the technology in the treatment pathway and Appendix C. Since the majority of people with GCA experience signs and symptoms up to 18 months after diagnosis, a treatment continuation rule has also been modelled here for tocilizumab. The base case analysis incorporates tocilizumab treatment, according to the anticipated Marketing Authorisation dosing schedule (QW – weekly dosing) until treatment discontinuation at 24 months. UK clinical expert opinion (see section B.1.3 Health condition and position of the technology in the treatment pathway and the NICE scope describe current treatment for GCA with GCs often being for 18-24 months continuous treatment.

The costs and consequences of these treatment rules for GC and tocilizumab are given in detail in section B.3.6 Summary of base-case analysis inputs and assumptions. Since the

mainstay of current GCA treatment is GC, which are known to have risk of serious AEs even at low doses, current clinical practice is to withdraw treatment as early as possible, without risking a GCA relapse/flare. Therefore, it is anticipated that this approach to treatment discontinuation is both clinically appropriate for the majority of patients, and also implementable for the NHS and clinicians (B.1.3.7 External expert input).

Monitoring costs are associated with patients receiving tocilizumab – these have been included in the model - however the monitoring costs associated with methotrexate and some other concomitant medications required by GCA patients which have an AE profile, have not been include (B.1.3.7 External expert input).

Costs savings for GCA patients receiving tocilizumab are expected from the avoidance of flares and the avoidance of GC-related AEs.

A sensitivity analysis to the duration of tocilizumab treatment continuation will be included in section B.3.6 Summary of base-case analysis inputs and assumptions, to allow consideration of the impact of the time to withdrawal on the cost-effectiveness.

GC dosing in combination with tocilizumab is included as per the GiACTA trial which uses a 26-week tapering regimen for the tocilizumab group (in contrast with the placebo group which has a GC taper regimen of 52 weeks).

Use of immunosuppressants is included in line with the treatments and doses used with the GiACTA trial.

More information on the implementation of the technologies in the cost-effectiveness model is provided in section B.3.5 Cost and healthcare resource use identification, measurement and valuation.

B.3.2.4 Disutility application for GCA-related complications and GC-related AEs

Utility decrements are applied to the model's baseline utility ('on remission' states) for patients who develop GCA-related complications or GC-related AEs. There are three standard approaches combining health utility information as it is mentioned in (Ara and Wailoo 2012): the additive, multiplicative and minimum methods. However, these methods have not been validated.

The additive approach uses the utility for a single health state and applies the marginal disutility for each additional state. Marginal disutility refers to the difference in utility between patients in a specific state of health and those not in that health state. Applying this approach

relies on the assumption that there are no interactions among the health states. This assumption is not applicable in this tocilizumab model for GCA treatment since the AEs occur in patients simultaneously while they have GCA as a diagnosis.

The multiplicative approach multiplies individual health state utilities in order to derive a single health utility. This approach assumes that the individual utility for each of the states applies, and that the result of being in multiple health states is a joint health state with lower utility than any of the individual states. This approach was applied in the model since it was considered the most appropriate, and allows a conservative estimate of the impact of GCA-related complications and GC-related AEs.

Finally, the minimum approach involves assessing the utilities for individual health states and using the lowest utility to represent the joint health state. This approach was not taken as it did not seem to reflect the aetiology of GCA, and the complications and AEs that can occur in this patient group.

Table 32 summarises the utility decrement for each AE applied in the model, derived from Luqmani et al. 2016. (Luqmani et al. 2016) Utility decrements are applied for all the GCA-related complications included in the model, specifically vision loss, minor stroke, and major stroke. A previous NICE HTA evaluation for GCA has added together disutilities from GC-related AEs, such as fracture and diabetes, plus disutility from common GC side-effects. However, to avoid the risk of double counting disutilities here, no utility decrements are applied for GC-related AEs. The only GC-related disutility applied in the model is in relation to: common side-effects of GCs (including weight gain, 'moon-shaped' facial appearance and frequent follow-up appointments); fracture; psychiatric disturbance; infections. (Niederkohr and Levin 2005) These were the same GC-related AEs discussed with the external experts at the advisory board (see B.1.3.7 External expert input). Once again, this is a conservative approach to measuring the benefits of tocilizumab to treat GCA.

Table 32: Utility decrements applied in the cost-effectiveness model

Disutility source	Utility Decrement Type	Utility decrement	Variance
GCA-related complications	Vision loss decrement on baseline utility	-0.36734	0.00184
	Minor stroke decrement on baseline utility	-0.17882	0.00089
	Major stroke decrement on baseline utility	-0.49122	0.00246
Common GC side effects	Common side-effects caused by GCs and mechanics of GC treatment	-0.07	None

B.3.3 Clinical parameters and variables

Clinical parameters for the model are derived from the pivotal GiACTA trial data for: time to first flare; cumulative steroid dose; utility on flare; and utility on remission. The GiACTA trial completed the 52-week follow-up in April 2016, and the analysis of the 104-week open-label extension will be available after the last patient last visit in April 2018.

In order to meet the NICE reference case requirements and model the cost-effectiveness of tocilizumab over a lifetime, additional clinical parameters are required outside of the GiACTA trial. These include an extensive study of CPRD data (Wilson et al. 2017a, 2017g), a previously published GCA HTA for GCA diagnosis (Luqmani et al. 2016), published GCA literature (Niederkohr and Levin 2005), UK clinician advisory boards (B.1.3.7 External expert input) and market research (Research Partnerships 2017).

The GiACTA trial had 2 GC only (control) arms, with a 26 week taper and 52 week taper, respectively. Since the 26 week taper is more rapid than tapering regimens recommended by the BSR guidelines, all data and comparisons below are against the 52 week GC tapering regimen. Similarly, the GiACTA trial had 2 tocilizumab (treatment) arms, weekly (QW) and bi-weekly (Q2W) treatment arms, but since CHMP Positive Opinion only references the weekly dosing regimen only these data have been modelled for cost-effectiveness.

The clinical parameters and variables to be discussed here include: transition probabilities; GC dose; GCA-related complications; GC-related AEs; and mortality.

B.3.3.1 Summary of transition probabilities

The transitions used in the model and the data sources are summarised below in Table 33 and are discussed in more detail in the following sections.

Table 33: Health state transitions

Transition	Transition probability	Source in submission
Remission to relapse/flare	Time dependent, calculated from GiACTA trial data of the time to first flare event	B.3.2.2. Model structure
Remission (escape) to subsequent relapse/flare	Constant, calculated from GiACTA trial data with extrapolation based on clinical opinion and published literature	
GCA-related complications from relapse/flare (vision loss and stroke)	Derived from GCA-related literature, as these serious but rare events didn't occur in the GiACTA trial with sufficient frequency to model	
GC-related AEs from all states receiving GC (fractures and diabetes)	Rate of developing GC-related AEs is matched to the CPRD study for GCA patients in the UK. These serious but rare events did not occur in the GiACTA trial	
Death from any state	No deaths occurred during the GiACTA trial, so mortality rates are linked to national statistics and relevant stroke literature	

The transition probability from remission to flare differs between the first and subsequent flares. Therefore, the cost-effectiveness model has separate transition probabilities for transitioning from remission to first flare and to subsequent flares. There are several reasons for this distinction, including:

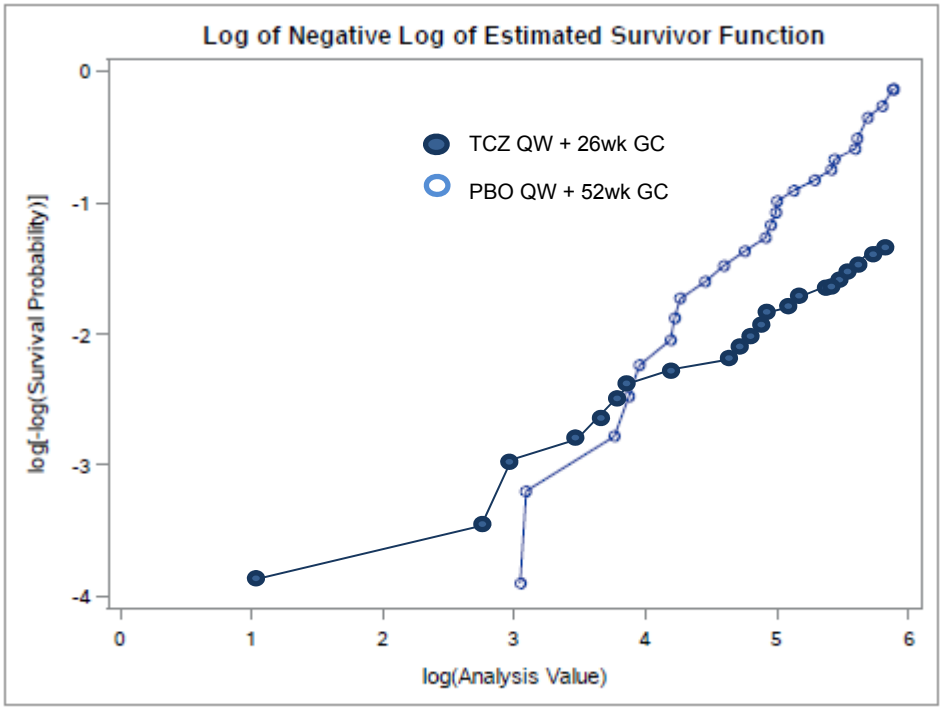
- allowing inclusion of both time dependence and more granular use of the clinical data, using the Kaplan-Meier curves for the time to first flare from the GiACTA trial where data are the most robust;
- in line with clinical expectation, analysis of the GiACTA data indicated a statistically significant difference in the transition to first and to subsequent flares
- prednisone dosing differs for relapsed patients, meaning that GC-related AEs are expected to be increased

B.3.3.2 Time to first flare transition probability

Different parametric models were applied to the Kaplan-Meier curves of time to first flare (TTFF). Following standard NICE guidelines in economic evaluation (Latimer 2013), the log-cumulative hazard plots were generated for the two treatment arms modelled from GiACTA (see Figure 10).The plots were not considered as parallel (notably the TCZ QW and PBO

QW + 52-week arms were intersecting), therefore, fitting individual parametric models to each treatment arm was the best approach.

Figure 10: Log of negative-log of estimated survivor function



Different parametric models were fit, and the goodness of fit assessment was based on both the statistical index of Akaike Information Criterion (AIC) and visual inspection.Table 34 shows the AIC estimates for each treatment arm and each separate parametric model that was assessed. The shadowed cells indicate the model that was selected as the base case, which is the Weibull for TCZ QW arm and the Exponential for the other arms. The normal decision criterion is to select the model with the lower AIC.

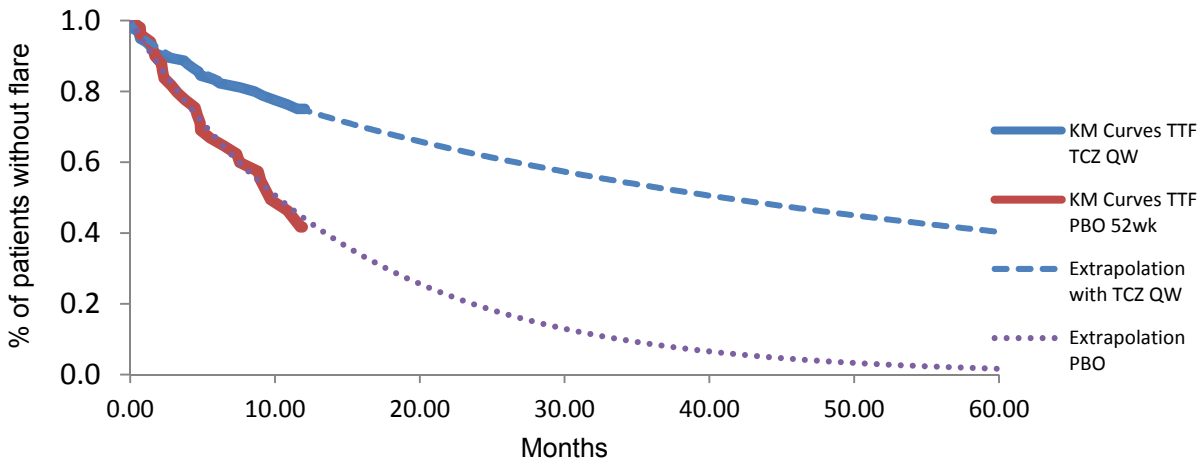
The results of the chosen parametric extrapolation methods were validated by comparing the proportion of patients on sustained remission to the expert clinical opinion (see section B.1.3.7 External expert input), and market research. (Research Partnerships 2017) These were suitably comparable since both these approaches estimated 15% - 20% of patients would achieve sustained remission, which is reflected in the model output

Table 34: AIC for parametric fit on TTFF

	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper
EXPONENTIAL	176.33073	118.04365
WEIBULL	174.88006	119.03899
LNORMAL	175.02922	118.10141
GAMMA	176.82294	118.10068
LLOGISTIC	174.90303	118.81808

Figure 11 illustrates the KM curves for each treatment arm and the base case parametric models of extrapolation: Weillbull for TCZ QW + 26-week GC taper and exponential for PBO QW + 52-week GC taper groups.

Figure 11: Parametric extrapolation of time to first flare (GiACTA data)



The piecewise extrapolation is included in the model for comparison, but has a worse fit than the parametric extrapolation.

B.3.3.3 Time to subsequent flare transition probability

The rate of subsequent flares was estimated from the GiACTA data, using a Poisson regression. The time frame of the analysis was defined from the time of the first flare for each individual patient until the end of the follow up, in order to observe the number of subsequent flares within the defined timeframe. The rate of subsequent flares for each treatment arm was normalised by using the average time after first flare and until the end of the follow-up, as observed for each treatment arm in the GiACTA trial (B.2.6.3 Annualised Relapse Rate).

Finally, the rates were converted to weekly transition probabilities in order to fit the model cycle of 7 days. Here it is clear to see that the weekly probability of subsequent flare is substantially higher in the control arm than in the tocilizumab arm demonstrates the transition probability from remission to subsequent flare for each treatment arm, here it is clear to see that the weekly probability of subsequent flare is substantially higher in the placebo 52 week control arm.

Table 35: Transition probability to subsequent flares calculated from GiACTA trial data

Treatment arm	Mean rate (in log scale)	Standard Error	Mean days follow-up used within the analysis	Weekly probability of flare
Tocilizumab QW	-1.056	0.354	228	0.0106
Placebo 52 week	-0.300	0.224	224	0.0228

Given the short duration of follow-up from the clinical trial, the transition probabilities for subsequent flare are reduced over time in the cost-effectiveness model, to reflect that many people with GCA do not require treatment continuously. However, the annual reduction in probability of subsequent flares over time is at zero, to reflect that flares can occur many years after initial diagnosis. (Andersson, Malmvall, and Bengtsson 1986) The tocilizumab treatment duration is set at 2 years to reflect the NICE scope and decision problem, but also to reflect published literature for current treatment duration. (Warrington 2014)

B.3.3.4 Prednisone dose for each treatment arm is based on GiACTA trial data

The GiACTA trial showed that tocilizumab has a clinically meaningful and statistically significant steroid-sparing effect in people with GCA (B.2.6 Clinical effectiveness results of the relevant trials). Reducing the dose of GC needed to avoid a GCA relapse/flare while managing GCA signs and symptoms is a major contribution of tocilizumab to the quality of life of people with GCA, since both high-dose and long-term steroid use are linked with serious AEs, particularly for elderly patients (see section B.1.3.3 Current treatment). Therefore, the model incorporates the steroid-sparing effect measured in the GiACTA trial and extrapolates the GC dose for the patients in each treatment arm.

The cost-effectiveness model estimates the cumulative GC dose for each treatment arm in three stages, specifically:

- **During primary remission (until first flare)**: Patients receiving tocilizumab, during their primary remission (e.g. until first flare) follow the 26 week GC tapering - as

defined in the GiACTA protocol. Similarly, patients in the placebo arm, follow the 52 week GC tapering - as defined in the GiACTA protocol

- **During secondary remission (after first flare)**: Based on the GiACTA protocol, patients who flare for the first time switch to the “escape” GC tapering regimen as per the investigator’s judgment. Therefore, a logistic growth regression was applied to the tocilizumab arm for GiACTA patients who had their first flare and switched to the escape regimen of GC use. In the regression, the predictive coefficient is time, in order to predict and extrapolate the tapering of GC, as observed in the trial. For the placebo 52 week arm, a similar logistic growth regression was applied based on the Real World Data from the Market Scan database, in order to capture the dose intensity and the duration of administration as it occurs in clinical practice.

[redacted]

Table 36: Cumulative GC dose equation parameters - tocilizumab arm, using GiACTA data

	Estimate	Standard error	t value	Pr(>|t|)
Asymptotic parameter	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]

Table 37: Cumulative GC dose equation parameters - GC arm, using Market Scan data

	Estimate	Standard error	t value	Pr(>|t|)
Asymptotic parameter	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]

- **During relapse/flare**: A predictive equation of the GC dose increase due to the relapse/flare was estimated per treatment arm, based on GiACTA trial data. The last effective dose is the prediction coefficient of the size of the GC dose increase due to flare. This increased GC dose is maintained for a week. This was an assumption that was considered to be conservative based on clinical input and given the acute nature of the event.

[redacted]

Table 38: Predicted GC dose increase for flare event

	Estimate	Standard error
Tocilizumab arm coefficient	[redacted]	[redacted]
GC arm coefficient	[redacted]	[redacted]

Prior to first flare and whilst on flare GC doses from the GiACTA trial are used for both arms directly within the model in order to ensure that costs and effectiveness are drawn from the same source where data is available.

The GiACTA GC dose tapering regimen represents the most favourable scenario in clinical practice – based on the BSR Guidelines (Dasgupta et al. 2010). If a patient in clinical practice experiences a relapse/flare then the GC dose is increased to re-gain control of the GCA and eliminate the GCA signs and symptoms in the patients, resulting in a higher cumulative steroid burden in clinical practice than in the GiACTA trial and the cost-effectiveness modelling presented here. A scenario analysis for GC cumulative burden is presented in section B.3.8.3 Scenario analysis to adhere to the equation-based GC dose.

Figure 12 and Figure 13 show the cumulative and weekly GC dose respectively, for each treatment arm, as predicted from the cost-effectiveness model, based on the assumptions above.

Figure 12: Cumulative GC dose predicted by the cost-effectiveness model

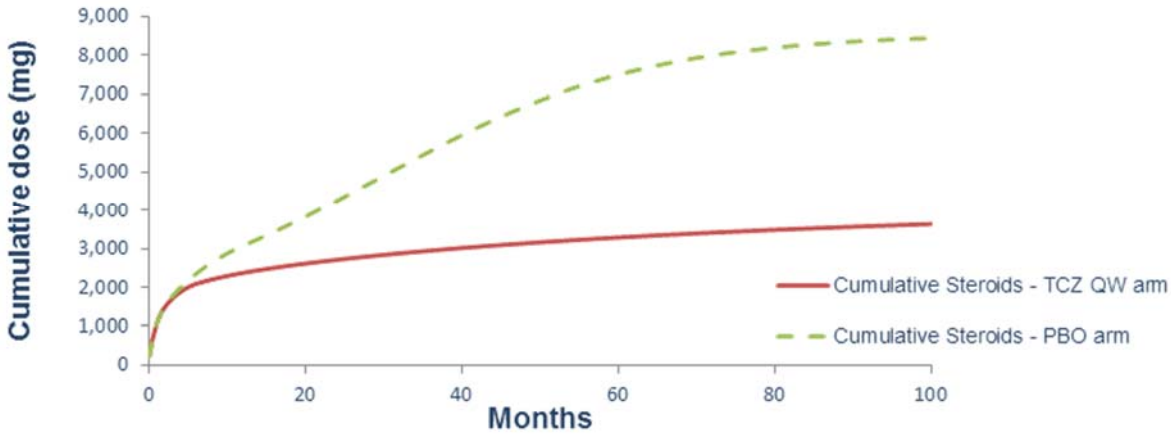
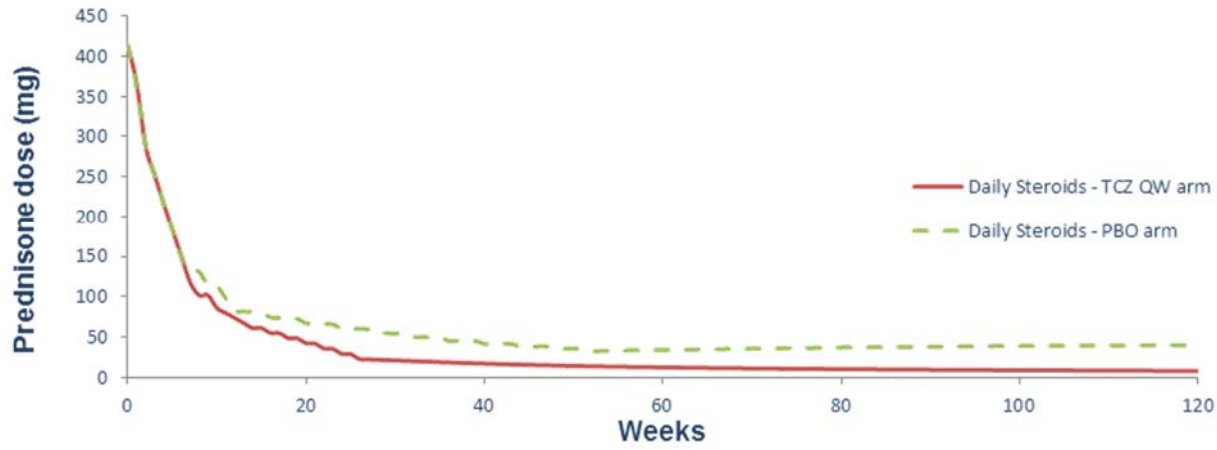


Figure 13: Weekly GC dose predicted by the cost-effectiveness model



B.3.3.5 Risk of GCA-related complications

Within the economic model, GCA-related complications can only be experienced by patients in the relapse/flare state. Since these rare but serious complications did not occur during the GiACTA trial, the rate of occurrence is modelled on the intermediate outcome of a relapse/flare event – which was measured directly during the GiACTA study. The rate of relapse/flare is then extrapolated over a lifetime risk using published GCA literature to estimate the risk from an HTA study comparing GCA diagnostic approaches. (Luqmani et al. 2016)

Loss of vision plus stroke are considered to be the most likely and relevant GCA-related complications for a person in relapse/flare (with a proportion of major strokes resulting in death). The annual incidence rates for these GCA-related complications are based on the HTA assessment of GCA diagnostic techniques by Luqmani *et al.* (Luqmani et al. 2016) The annual incidence rates reported in Table 39 were converted to weekly probabilities to fit the 7 day cycle length of the model.

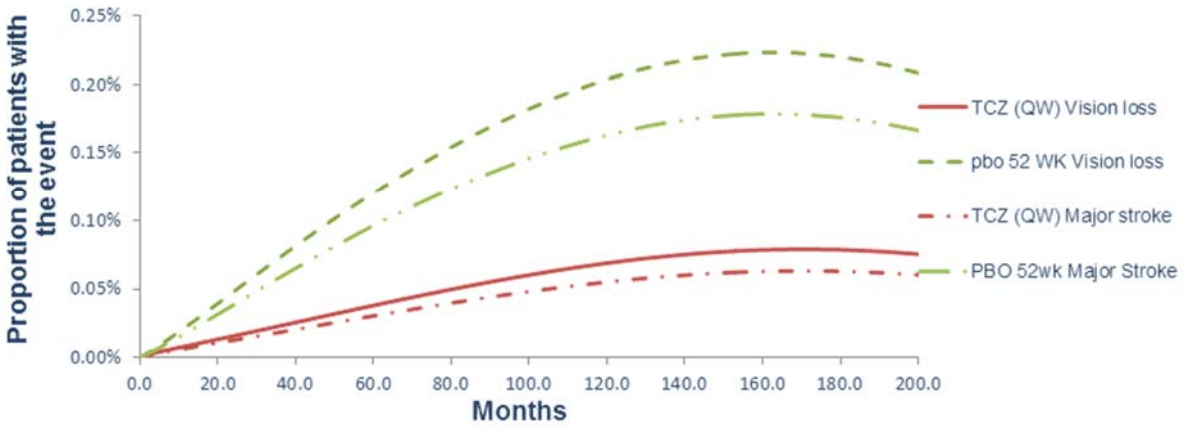
Figure 14 presents the proportion of patients who have developed GCA-related complications over time within the model.

Table 39: GCA-related complications

Variable	Annual incidence rates	Comment
% of GCA patients with visual complications at flare	0.013	
% of GCA patients with stroke at flare	0.026	Assuming that from the 2.64% of strokes, 60% are minor and 40% are major

(Luqmani et al. 2016)

Figure 14: Proportion of patients with GCA-related complications



B.3.3.6 GC-related AEs are associated with cumulative GC burden

Since GC are the mainstay of treatment currently for people with GCA, and both high-dose and long-term GC are related to serious AEs, these are extrapolated in the cost-effectiveness model. Numerous AEs are known to be associated with GC treatment; however, only fractures, diabetes mellitus, osteoporosis and infections were included in the model, since they were considered the most relevant based on advice from clinicians*, review of GCA-relevant literature (van der Goes et al. 2010), and importance in terms of NHS costs. (See Figure 15 and Figure 16.)

The rate of GC-related AEs in the GiACTA trial was too low, so the lifetime risk of these occurring was linked to the intermediate outcome of cumulative GC dose - which was measured from the GiACTA trial and then extrapolated over a lifetime risk to derive the event rate. The most important AEs for GCA patients treated with GCs have been studied via the extensive CPRD analysis, conducted by Roche, and an incidence rate has been calculated based on the incremental associated risk of the event, in relation to different segments of the cumulative GC dose received. (Wilson et al. 2017a, 2017g)

In order to ensure the GC-related AE rate was relevant to UK clinical practice, the cumulative GC dose used in the model was set to that reported from the CPRD database, however it is important to recognise that given a large proportion of the extreme treatments are prescribed by consultant rheumatologists, this CPRD value may be an underestimate. (Petri et al. 2015) The importance of this is explored as a sensitivity analysis in section B.3.8.3 Scenario analysis.

* See section B.1.3.7 External expert input

Figure 15: GC-related AEs: diabetes and osteoporosis

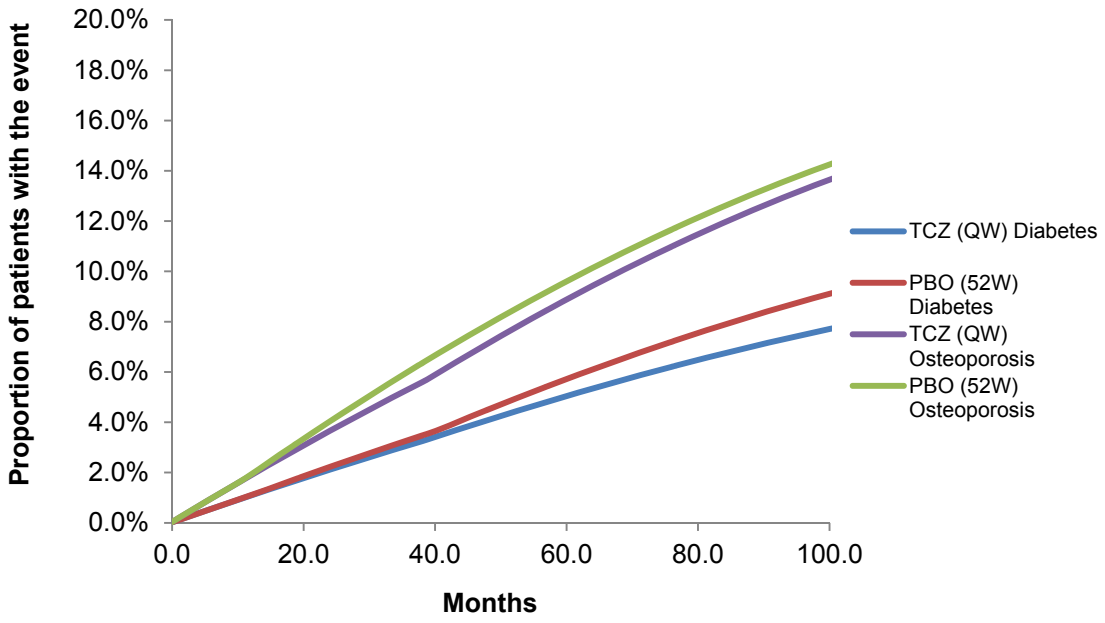
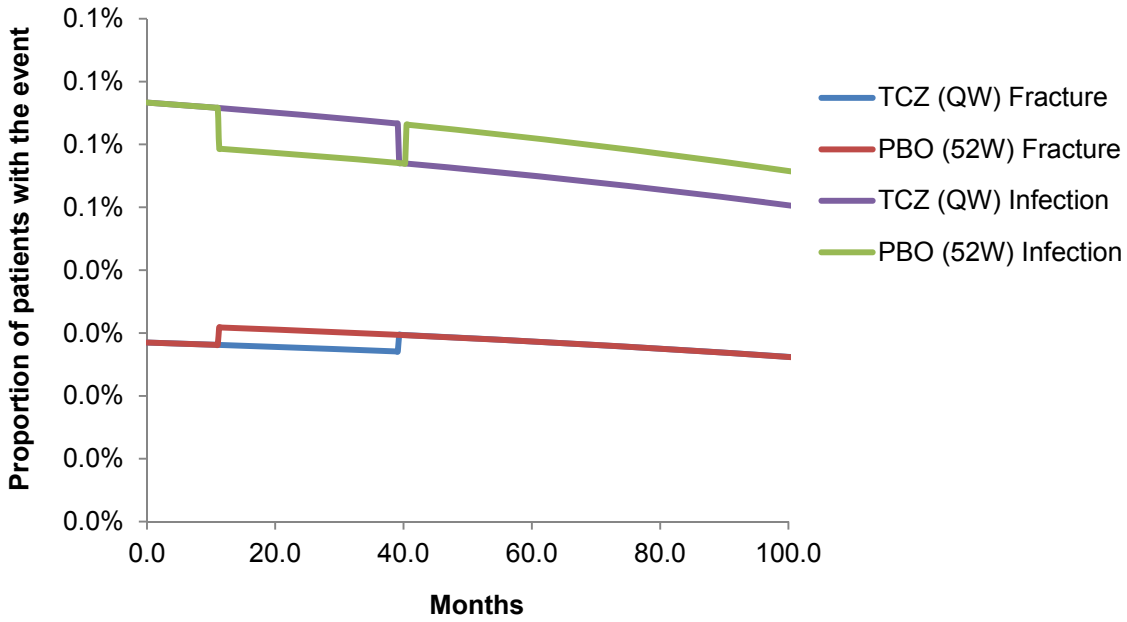


Figure 16: GC-related AE: fracture and infection



B.3.3.7 Tocilizumab-related AEs

AEs related to tocilizumab are not modelled separately since there was no clear increase in AEs in the tocilizumab arms of the GiACTA trial (B.2.10 Adverse reactions). Therefore, if AEs were assigned to both GC and tocilizumab, the probability of double counting the safety issues in the GiACTA trial was considered to be significant. This is emphasised even more

since the grade and frequency of AEs between the tocilizumab and placebo treatment arms were not substantially different. Furthermore, since no additional safety issues were identified in people with GCA on tocilizumab in the GiACTA trial, tocilizumab-related AEs were not modelled separately.

AEs were not modelled within the economic analysis since the incidence of AEs was very similar across all treatments in the GiACTA trial. Also, given GiACTA is a head-to-head trial, it was assumed that the costs of treating an AE would be the same in all arms compared and therefore the cost-effectiveness ratios would not be affected by these costs.

B.3.3.8 Background mortality

The model incorporates background mortality for all patients based on UK lifetables. (Office of National Statistics 2016) No direct GCA mortality is incorporated in the model. This is primarily because no deaths occurred during the follow up period of the GiACTA trial, but also because literature (primarily the recent systematic literature review and meta-analysis from Hill et al. (Hill et al. 2017)) indicates that long-term mortality is not increased in GCA (discussed in more detail in section B.3.2.2. Model structure. However, mortality indirectly due to GCA is incorporated via the occurrence of major strokes during a flare, where 50% of the patients with such an event will die in the model. (Luqmani et al. 2016) Stroke related mortality was deducted from the background mortality rates using national estimates, in order to avoid double counting.

B.3.3.9 Stroke related mortality

The rate of stroke related mortality was assumed to be 50% based upon. (Luqmani et al. 2016)

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

As part of the HRQoL systematic literature review, discussed in section B.2.1 Identification and selection of relevant studies, relevant clinical trials reporting HRQoL were identified.

In line with the NICE reference case, EQ-5D index data are considered the preferred measure of utility elicitation. EQ-5D index data were collected in the GiACTA clinical trial (see B.2.6.5 Health related quality of life). No other clinical trials reported EQ-5D index data.

From the SLR conducted on 8 May 2017, only two trials (Spiera et al. 2001; Stone et al. 2017)) assessed HRQoL using SF-36 at baseline and 52-weeks. Spiera et al. assessed

methotrexate compared to placebo with tapering corticosteroids and the GiACTA trial assessed tocilizumab compared to placebo, both with GC taper. Spiera et al. reported no data and only the mental and physical component scores were reported from the GiACTA trial. The SF-36 results from the GiACTA trial were published on the Clinical Trials website; these are presented in section B.2.6.5 Health related quality of life and are summarised in Appendix H1.2.

Table 40: Study details for included HRQoL trial

Author, year	Title	Country	Study design	Study duration	Treatment	SF-36 (SD)
GiACTA trial via Clinicaltrials.gov	An Efficacy and Safety Study of Tocilizumab (RoActemra/Actemra) in Participants With Giant Cell Arteritis	Austria, Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Portugal, Spain, Sweden, United Kingdom United States	Multicenter, randomised, double-blind, placebo-controlled, parallel-group study	52 weeks	Patients with GCA Tocilizumab QW + 26 Weeks Prednisone Taper: n= 97 Tocilizumab Q2W + 26 Weeks Prednisone Taper: n= 49 Placebo + 26 Weeks Prednisone Taper: n= 48 Placebo + 52 Weeks Prednisone Taper: n= 49	Tocilizumab QW + 26 Weeks Prednisone Taper: n= 97 MCS: Baseline: 42.77 (12.43) Change at 52 weeks (n=59): 8.21 (10.35) PCS: Baseline: 43.10 (9.43) Change at 52 weeks (n=59): 5.37 (7.38) Tocilizumab Q2W + 26 Weeks Prednisone Taper: n= 49 MCS: Baseline: 47.67 (12.59) Change at 52 weeks (n=26): 1.98 (7.17) PCS: Baseline: 40.62 (8.00) Change at 52 weeks (n=26): 2.71 (8.86) Placebo + 26 Weeks Prednisone Taper: n= 48 MCS: Baseline: 42.73 (12.13) Change at 52 weeks (n=9): 4.99 (7.54) PCS: Baseline: 42.65 (10.87) Change at 52 weeks (n=9): 2.08 (12.11) Placebo + 52 Weeks Prednisone Taper: n= 49 MCS: Baseline: 40.45 (13.73) Change at 52 weeks (n=18): 2.60 (10.56) PCS: Baseline: 41.12 (9.97) Change at 52 weeks (n=18): -2.80 (6.98)

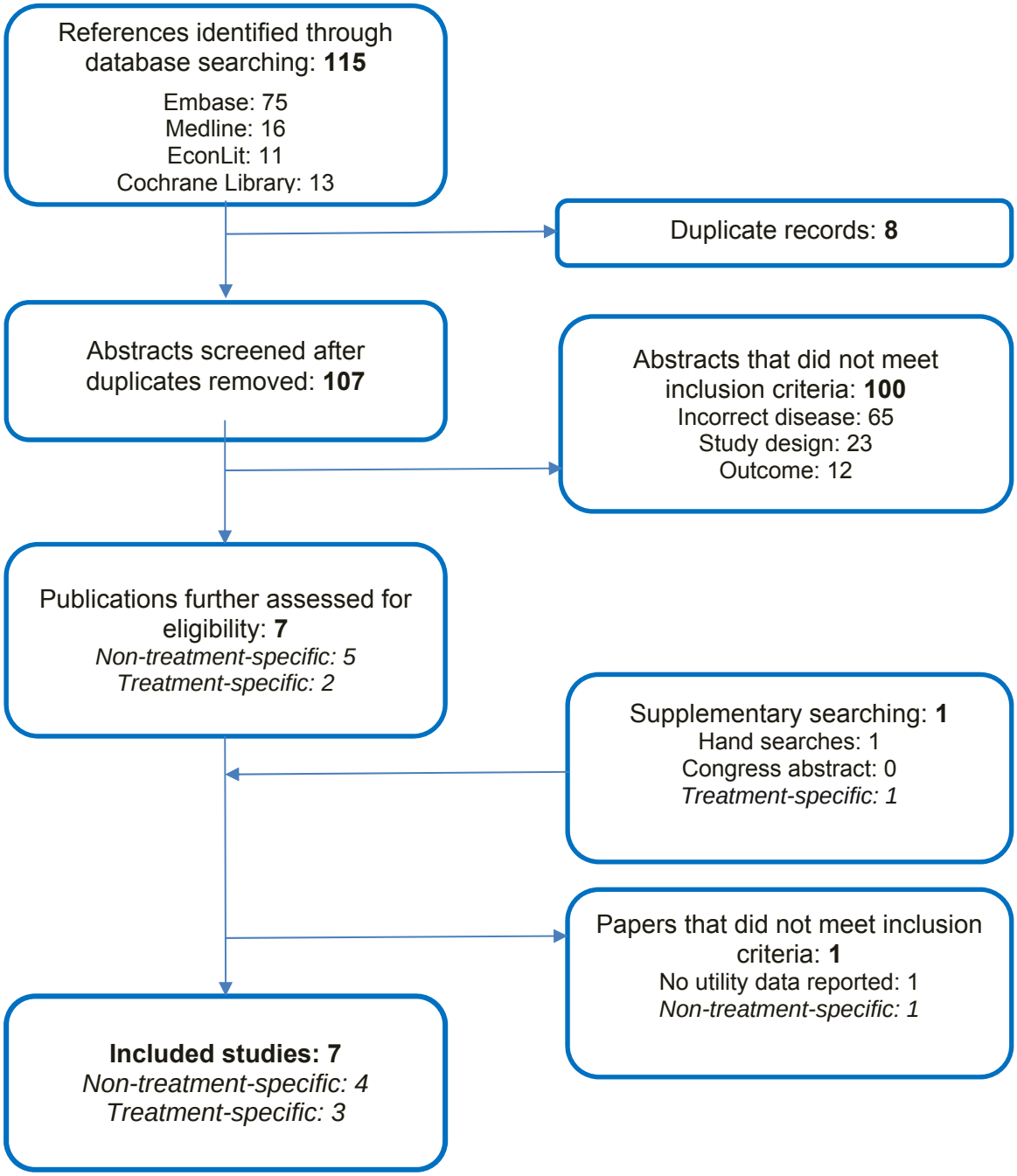
B.3.4.2 Mapping

As EQ-5D data was available from the GiACTA trial mapping was not required.

B.3.4.3 Health-related quality-of-life studies

A comprehensive SLR was performed to identify HRQoL data associated with GCA (see Appendix H for details). Searches were based on the filters provided by Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Guidelines Network (SIGN)) and the InterTASC Information Specialists' Sub-Group (ISSG) (Lekander et al.). Searches were run on the 8th May 2017 and screening was performed double-blind. Figure 17 presents the PRISMA flow diagram, showing the attrition rate at each stage of the review.

Figure 17: PRISMA flow diagram of included HRQoL studies



Seven studies were identified by the systematic review of publications for health-related quality of life studies in patients with GCA. Three of these studies were treatment-specific and were also identified in the clinical systematic review; these studies have been presented in section B.3.4 Measurement and valuation of health effects.

Of the four further publications identified from the SLR (Kermani 2016) ; (Jobard et al. 2017) (Kupersmith et al. 2001; Elsideeg 2014) which assessed HRQoL in patients with GCA, three publications were full texts (Kermani 2016); (Jobard et al. 2017);(Kupersmith et al. 2001) and one was a congress abstract (Elsideeg 2014).

One publication reported EQ-5D VAS (Elsideeg 2014) and the remaining three publications reported SF-36 (Kermani 2016); (Jobard et al. 2017);(Kupersmith et al. 2001)

Two studies (Elsideeg 2014) (Kermani 2016) reported that the QoL of people with GCA was less than controls, as measured by SF-36 (Kermani 2016)and EQ-5D VAS mean health score (61.2/100 (range 45-80) (Elsideeg 2014). In contrast, one study reported GCA patients' SF-36 scores were not significantly different from controls, the authors suggested that quality of life was preserved in this population following treatment with high dose of corticosteroids (Jobard et al. 2017); however, this is contradictory to other published literature (Niederkohr and Levin 2005). One study reported that, whilst the baseline mental health component score (MCS) from SF-36 had a significant correlation with visual performance, the baseline overall SF-36 scores did not correlate with the presence or absence of visual loss (Kupersmith et al. 2001). Similarly, Jobard et al. concluded visual impairment caused by GCA does not seem to have any major impact on QoL (Jobard et al. 2017). The authors suggested this could be because there are no questions in the SF-36 questionnaire assessing vision. Kermani et al. also reported that the SF-36 MCS scores appeared not to differ depending on disease or health status (Kermani 2016).

In contrast, the published HTA evaluation for GCA diagnostic techniques assigned disutility to both vision loss and GC use (Luqmani et al. 2016), summarised in B.3.2.4 Disutility application for GCA-related complications and GC-related AEs.

Given the paucity of utility evidence returned from the SLR, articles excluded due to not meeting the selection criteria were further evaluated. Two articles initially excluded at the stage of 'title and abstract' due to being related to diagnostic approaches (Luqmani et al. 2016) or undiagnosed but suspected GCA (Niederkohr and Levin 2005) reported utility values for further consideration during this cost-effectiveness appraisal.

B.3.4.4 Adverse reactions

No utility data on the impact of AEs on HR-QoL were reported in the studies found within the SLR (although utility decrements for AEs in GCA patients were reported in the GCA diagnosis HTA publication (Luqmani et al. 2016)).

As summarised in B.3.2.4 Disutility application for GCA-related complications and GC-related AEs, utility decrements are only applied to GCA-related complications and to the disutility associated with common side-effects of GCs, this conservative approach was taken to avoid the risk of double counting utility decrements.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities

All the people enrolled in the GiACTA trial completed the EQ-5D-3L questionnaire at baseline and at weeks 12, 24, 36 and 48 (B.2.6.5 Health related quality of life). Standard UK tariffs were used for clinical validation. (Dolan 1997) Whilst a significant treatment benefit was not shown on the EQ-5D-3L significant benefits were seen within other quality of life measures included in the study (patient global assessment and SF-36 physical component). The 4-week duration of impact on the patient's quality of life of a relapse/flare does not match the frequency of planned EQ-5D assessments, requiring further analysis of the data provided.

Remission and relapse/flare health state utilities were calculated from GiACTA trial data using a mixed effects model, adjusting for baseline utility. No time component was included as no trend in terms of utility change over time was observed in the GiACTA trial. A mixed effects model was used to account for the correlation of utility reporting within individuals.

Data were combined across all treatment arms within the regression model as no significant difference in quality of life by treatment arm was reported within the clinical trial.

Table 41 shows the utilities calculated from GiACTA data and Figure 18 illustrates the consistency across treatment arms for the lower utility when patients relapse/flare. These data clearly show the utility for a person with GCA on flare is significantly lower that the utility on remission. A flare event was determined by the investigator and was defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA.

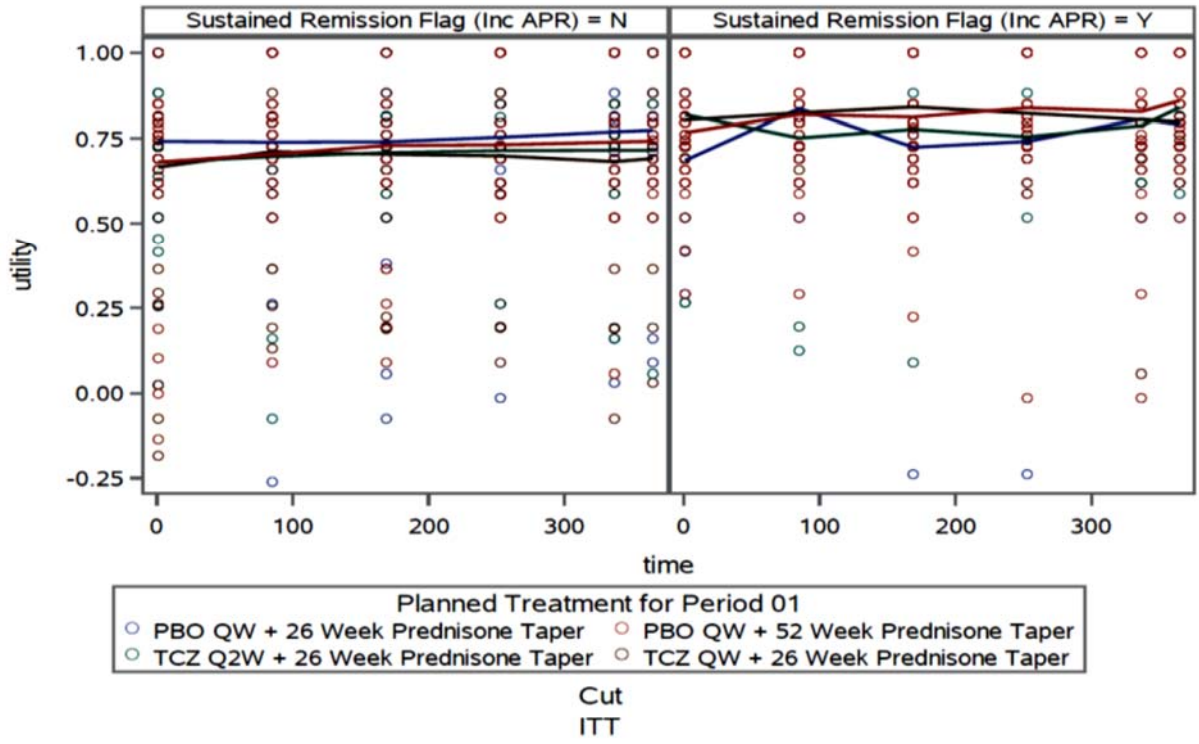
The flare events were rare and short-lived in the GiACTA trial and only the first flare was calculated because second flare events were less likely to occur. Therefore, flare events were averaged across all four treatment arms in the GiACTA trial in order to increase the

robustness of any analysis. In addition, the impact of a flare event on a patient's quality of life is expected to be no different across treatment groups. B.1.3.7 External expert input

Table 41: Utilities from GiACTA trial used in the cost-effectiveness modelling

Health State	Estimate	Std. Error	P-Value	Lower 95% CI	Upper 95% CI	Justification
On remission	0.7713	0.00667	<0.0001	0.7582	0.7844	GiACTA data
On Flare	0.6420	0.02447	<0.0001	0.5940	0.6901	GiACTA data

Figure 18: EQ-5D values from the GiACTA trial for people in remission or relapsing/flaring

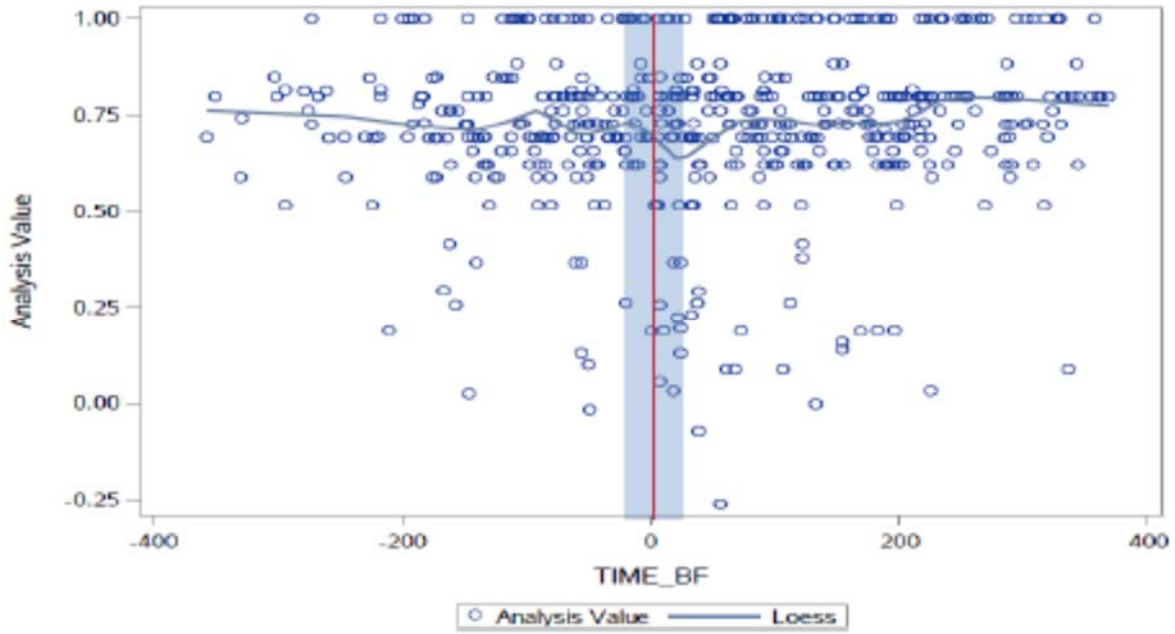


Duration of flare disutility

The reduced QoL observed for patients experiencing a relapse/flare was applied in the model for 28 days, since 28 days was the mean duration of a flare reported from third-party market research of clinicians across several specialities treating GCA in the UK. (Research Partnerships 2017) This duration of flare disutility is considered further in the section B.3.8 Sensitivity analyses as a sensitivity analysis. Figure 19 demonstrates the consistency of available market research of clinical opinion with a drop in utility shown of over 30 days around the time of flare analysed from the GiACTA trial. The horizontal axis of the graph is time to flare (negative times) and time from flare (positive times) where 0 is the actual time when flare was reported. The vertical axis shows the utility weight. The dots represent

individual point values (the same patient can have multiple time visits) and the solid line is a smoother measure (e.g. Lowess). The blue shading indicates the range of days before and after a flare event where the highest shift from baseline utility weight was observed.

Figure 19: Change in utility before and after a relapse/flare



Disutility application for GCA-related complications and GC-related AEs are presented in B.3.2.4 Disutility application for GCA-related complications and GC-related AEs.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

In appendix I describe how relevant cost and healthcare resource data were identified.

B.3.5.1 Intervention and comparators' costs and resource use

The costs of treating GCA patients with either tocilizumab + GC or GC alone are presented below in Table 42.

The cost of GC treatment varies greatly for people with GCA, depending on their stage of taper, as well as whether they are relapsing/flaring or in remission B.1.3 Health condition and position of the technology in the treatment pathway. According to the BSR Guidelines, the peak dosage to treat relapse/flare is 60 mg/day, which for prednisone would give a monthly cost of £325.07 – it is unlikely that many patients would be on 60 mg/day prednisone for very long. In contrast, the BSR Guidelines recommend 5 mg/day for maintenance doses, which for prednisone would cost £27.09 for a month. The average

cumulative dose of 8.6 g reported from the CPRD analysis of GCA patients would cost £1,210.40 for prednisone.

Due to this variation in recommended treatment approach the costs presented below represent first year costs.

Table 42: Costs of tocilizumab and GC for treating people with GCA

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

B.3.5.2 Health-state unit costs and resource use

The unit costs and resource use associated with the 7 different health states within this cost-effectiveness model are described in Table 46.

The costs associated with health and social care are all cited from the PSSRU 2016.(Curtis 2016)

Disease management costs

Disease management costs have been calculated separately for the following health states:

- Patients ‘on remission + on steroid’;
- Patients ‘on remission + off steroid’;
- Patients ‘on flare / relapse’;
- Patients ‘on remission + on maintenance steroids’.

Management costs per flare event were included in the economic model based on data collected in the UK market research study conducted by Roche (Research Partnerships 2017).

The market research suggested the average number of appointments per flare event is 2.71. (Research Partnerships 2017) The proportion of patients seen by each type of physician at initial presentation and within later treatment alongside the average cost per visit is presented in Table 43.

Table 43: The proportion of patients seen by physician type at initial presentation and later with the average costs per visit

Management during flare	% of patients initially presenting to this speciality	% of respondents stating each physician time was involved in flare follow-up	Cost per visit	NHS reference cost code
GP	59%	44%	£36	10.3b PSSRU 2016 (Curtis 2016)
Rheumatologist	25%	67%	£137	410; Rheumatology (Department of Health 2016)
Opthalmologist	7%	10%	£58	460; Medical Ophthalmology (Department of Health 2016)
Geriatrician	2%	13%	£188	430; Geriatric Medicine (Department of Health 2016)
Neurologist	1%	6%	£161	400; Neurology (Department of Health 2016)
Other	7%	5%	£164	300; General Medicine (Department of Health 2016)

(Research Partnerships 2017)

The weighted average cost of visits was calculated based upon the physicians involved in initial presentation and later treatment as £259.77 in total per flare (cost of presentation = £76.11 and cost of each follow up visit = £107.40).

Based upon the same market research 33% of patient received methotrexate during flare, and accordingly this cost was included within the calculation of flare costs. The impact of

including this cost is tested within sensitivity analysis. The cost of methotrexate was assumed to be the same as the cost included within the concomitant medication calculations.

It should be noted that these costs are relatively conservative given that expert opinion for tocilizumab noted an expectation that all patients would eventually present to a hospital (i.e. more frequent and more costly visits than were predicted in the market research). It was suggested that the patients in the market research who are managed by primary care may just be late presenters back to hospital services (B.1.3.7 External expert input).These underestimates in appointment frequency may, however, be balanced out by uncertainty surrounding appointment cost (currently assumed face to face) as some clinics are known to conduct appointments over the phone.

The resource use costs associated with the on remission + on steroid, on remission and off steroid and on remission and maintenance steroids health states were also sourced from the UK market research study ((Research Partnerships 2017)).

The frequency and proportion of patients expected to receive specialist management for each health state is provided in Table 44.

Table 44: Frequency and proportion of patients expected to receive specialist management for each health state

Management Cost after diagnosis	% of patients	Cost per visit	NHS reference cost code
Rheumatologist	66%	£137	410; Rheumatology (Department of Health 2016)
GP	17%	£36	10.3b PSSRU 2016 (Curtis 2016)
Geriatrician	10%	£188	430; Geriatric Medicine (Department of Health 2016)
Opthalmologist	5%	£58	460; Medical Ophthalmology (Department of Health 2016)
Neurologist	2%	£161	400; Neurology (Department of Health 2016)
Other	1%	£164	300; General Medicine (Department of Health 2016)

(Research Partnerships 2017)

Unit costs per visit were sourced from NHS reference costs for each follow up visit and converted to ‘per cycle’ costs using the frequency of visits (Table 45) sourced from the market research study. The ‘per cycle’ costs were then applied to the proportion of patients

receiving each specialist visit to calculate the average resource use cost for each health state.

Table 45: Frequency of visits for GCA management

Management frequency	Proportion of frequency of follow up (on remission + on steroid)	Proportion of frequency of follow up (on remission + off steroid)	Proportion of frequency of follow up (on remission + on maintenance)
Weekly	4.72%	0.00%	1.92%
Every 2 weeks	14.64%	0.00%	9.70%
Monthly	25.94%	1.00%	24.33%
Every 2 months	12.97%	8.00%	13.48%
Every 3 months	21.26%	17.00%	26.15%
Every 6 months	13.06%	26.00%	16.78%

(Research Partnerships 2017)

In the base case, for each resource unit cost in the economic analysis, a cost multiplier was applied to reflect that GCA patients represent high cost patients. The multiplier was calculated as 1.58 using data provided in the PSSRU 2016 by dividing the average primary care cost of the top 25% high cost patients (£381.00) over the average primary care cost of all patients (£241.00).

Monitoring for tocilizumab requires ALT and AST levels, neutrophils and platelets and lipids to be tested every 4-8 weeks. (Hoffmann-La Roche Ltd. 2017a) These were assumed to be included within one blood test, applied as a management cost to all patients on tocilizumab treatment every 6 weeks. The cost of a blood test was assumed from NHS reference costs to be £3 (DAPS05 directly accessed pathology service: Haematology). The frequency of specialist contact was expected to remain the same for patients receiving both tocilizumab and current care.

The typical GC dose increase during flare has been taken from the GiACTA study initially.

The CPRD analysis showed that according to GP databases, the mean cumulative dose of GC for GCA patients requiring over 2 years of treatment was 8.6 g. (Petri et al. 2015). The average cumulative dose of GCs extrapolated within the model, based on Market Scan data, were therefore adjusted to a mean of 8.6 g, to best match estimates of UK clinical practice for the incidence rates of GC-related AEs. Since many stages of treatment for GCA requires consultant rheumatologist appointments, it is possible this CPRD mean is an under estimate.

For the GC-related AEs, the model considers a lifetime cost for patients with diabetes, while for the fractures a one-off cost per event is applied, calculated as the average cost of different types of fractures (vertebral, hip, proximal humerus and forearm), weighted by the annual risk of these fractures in the general population but age-matched to people with GCA.

For the few patients who suffer vision loss during their flare, the model applies a lifetime cost for the first and the subsequent years. Similarly, the patients with a non-fatal stroke also have a cost attributed to them for the following 5 years after the event.

Table 46: List of health states and associated costs in the economic model

	Tocilizumab	Prednisone
Tocilizumab cost	£18,291.37	£0.00
Prednisone Cost	£1,066.71	£2,253.10
Flare cost	£1,369.41	£3,728.13
GCA related costs	£65.30	£262.34
CS AE costs	£4,627.35	£4,920.52
Concomitant drug	£366.96	£14.05
Disease management	£9,924.63	£13,332.01
Total Costs	£35,711.73	£24,510.15

B.3.5.3 Adverse reaction unit costs and resource use

The adverse events costed within this model are linked to the health states of GCA-related complications or GC-related AEs, so are detailed in Table 46: List of health states and associated costs in the economic model.

B.3.5.4 Miscellaneous unit costs and resource use

All relevant costs for this model have been included in section B.3.5 Cost and healthcare resource use identification, measurement and valuation – no additional miscellaneous unit costs are included.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case model variables, for the *de novo* cost-effectiveness analysis of tocilizumab for GCA treatment, is presented in Table 47.

Table 47: Summary of model variables in the base case

Variable	Value	Measurement of uncertainty and distribution	Source
Age (years)	69.05	Not included in SA	GiACTA trial
Weight (kg)	70.75		GiACTA trial
Height	165.15		GiACTA trial
Time horizon (years)	30	Not included in SA	NICE reference case
Discount rate for costs and outcomes	3.50%		NICE reference case
Probability of first flare for tocilizumab QW arm: piece 1 of the piecewise extrapolation – 0-26 weeks	0.421	Normal SE: 0.016	GiACTA trial
Probability of first flare for tocilizumab QW arm: piece 2 of the piecewise extrapolation – 27 weeks to the end of GC treatment	0.213	Normal SE: 0.006	GiACTA trial
Probability of first flare for GC arm: piece 1 of the piecewise extrapolation – 0-26 weeks	0.832	Normal SE: 0.015	GiACTA trial
Probability of first flare for GC arm: piece 2 of the piecewise extrapolation – 27 weeks to the end of GC treatment	0.987	Normal SE: 0.052	GiACTA trial
Probability of relapse/flare from remission (on escape) for tocilizumab QW arm	Mean rate (in log scale):- 1.056 Mean days on escape: 228.39	Normal SE: 0.354	GiACTA trial
Probability of relapse/flare from remission (on escape) for GC arm	Mean rate (in log scale): -0.300	Normal SE: 0.224	GiACTA trial

	Mean days on scape: 224.77		
Probability of visual complications at relapse/flare	0.00025	Beta (12, 900)	(Luqmani et al. 2016)
Probability of stroke at relapse/flare	0.00050	Beta (60, 895)	(Luqmani et al. 2016)
Probability of minor stroke at relapse/flare	0.0030	Beta (60, 895)	(Luqmani et al. 2016)
Probability of major stroke at relapse/flare	0.0020	Beta (60, 895)	(Luqmani et al. 2016)
Probability of death from major stroke (in addition to background mortality from life tables)	50%	SE: 0.025 (assumption)	(Luqmani et al. 2016)
Fracture equation intercept	-2.6583	Normal SE: 0.0849	(Orfanos 2017)
Fracture equation slope	0.0746	Normal SE: 0.0275	(Orfanos 2017)
Diabetes with chronic complications equation intercept	-3.9216	Normal SE: 0.1346	(Orfanos 2017)
Diabetes with chronic complications equation slope	0.1297	Normal SE: 0.0373	(Orfanos 2017)
Baseline utility on remission	0.77130	Beta (3060.148,907.372)	GiACTA trial
Baseline remission on relapse/flare	0.64200	Beta (245.783,137.057)	GiACTA trial
GCA flare disutility	0.1293	Fixed	GiACTA trial
GC-related disutility	-0.03		(Niederkohr and Levin 2005)
GCA-related vision loss disutility from baseline	-0.36734	Beta (217.927,0.003)	(Luqmani et al. 2016)
GCA-related minor stroke disutility from baseline	-0.17882	Beta (754.201,0.001)	(Luqmani et al. 2016)
GCA-related major stroke disutility from baseline	-0.49122	Beta (105.394,0.005)	(Luqmani et al. 2016)

GC-related diabetes mellitus disutility from baseline	-0.09264	Beta (1777.372,0.001)	(Luqmani et al. 2016)
GC-related Vertebral body compression fracture (year1) disutility from baseline	-0.33179	Beta (269.152,0.002)	(Luqmani et al. 2016)
GC-related Hip fracture (year 1) disutility from baseline	-0.23915	Beta (484.138,0.002)	(Luqmani et al. 2016)
GC-related Proximal humerus fracture (year 1) disutility from baseline	-0.10772	Beta (1478.150,0.001)	(Luqmani et al. 2016)
OCS-related Forearm fracture (year 1) disutility from baseline	-0.09264	Beta (1777.372,0.001)	(Luqmani et al. 2016)
Weighted GC-related fracture* decrement in year 1	-0.2025	Weighted average of Beta distribution of each fracture type in year 1	(Luqmani et al. 2016)
GC-related Vertebral body compression fracture (>=yr.2) disutility from baseline	-0.26177	Beta (416.389,0.002)	(Luqmani et al. 2016)
GC-related Hip fracture (>=yr.2) disutility from baseline	-0.11526	Beta (1358.198,0.001)	(Luqmani et al. 2016)
GC-related Proximal humerus fracture (>=yr.2) disutility from baseline	0.00000	Beta (0.000,0.000)	(Luqmani et al. 2016)
GC-related Forearm fracture (>=yr.1) disutility from baseline	-0.01508	Beta (12864.486,0.000)	(Luqmani et al. 2016)
Weighted GC-related fracture* decrement in year 2 and onwards	-0.1128	Weighted average of Beta distribution of each fracture type in years 2 in advance	(Luqmani et al. 2016)
Tocilizumab subcutaneous formulation; 4x162 mg syringe	£913.12**	Not included in SA	BNF 2017
Prednisone (Lodotra); 30 tablets at 5 mg each	£26.70	Not included in SA	BNF 2017
Diabetes mellitus	£48.30	Normal SE: 0.15 (assumption: ±30%)	PSSRU 2016 (Curtis 2016)

	Cost	Weight	NA	
Vertebral body compression fracture	£1152	31.4%	NA	(Luqmani et al. 2016)
Hip fracture	£4222	22.3%	NA	
Forearm fracture	£690	32.5%	NA	
Proximal humerus fracture	£690	13.8%	NA	
Weighted fracture cost***	£1,624.09	Normal SE: 0.15 (assumption: ±30%)		
Treatment in primary care only	£115.56	Normal SE: 0.15 (assumption: ±30%)		Market Research (Research Partnerships 2017) PSSRU 2016 (Curtis 2016)
Primary care referral to specialist care	£568.88	Normal SE: 0.15 (assumption: ±30%)		Market Research (Research Partnerships 2017) PSSRU 2016 (Curtis 2016)
Vision loss – first year	£97.55	Normal SE: 0.15 (assumption: ±30%)		(Luqmani et al. 2016)
Vision loss – subsequent years	£93.97	Normal SE: 0.15 (assumption: ±30%)		(Luqmani et al. 2016)
Non-fatal stroke	£112.69	Normal SE: 0.15 (assumption: ±30%)		(Luqmani et al. 2016)

*Average disutility for the different types of fracture for year 1 and subsequent years, weighted by the risk of each fracture per annum in the general population, but age-matched to people with GCA. **List prices, PAS prices are stated in sections B.3.5.1 Intervention and comparators' costs and resource use. ***Average fracture costs is the weighted average of the different cost types, weighted by the risk of each fracture type per annum for the general population, but age-matched to people with GCA

B.3.6.2 Assumptions

In order for the GiACTA data to be built into a *de novo* cost-effectiveness model fitting the NICE reference case, a number of assumptions are required. A summary of these assumptions are presented in Table 48.

Table 48: Summary of assumptions

Variable	Assumption	Justification/notes
Utilities	Disutilities associated with flare, and common GC-related AEs are additive	These disutilities represent distinctly different health impacts so their effects can be combined with this approach. This approach has been taken previously in published literature (Ara and Wailoo 2012) (Luqmani et al. 2016)
Costs and resource use	The only GC-related AEs included in the model are for diabetes mellitus fractures, osteoporosis and infections, since these are reported to be the most relevant for GCA patients' QoL and NHS costs	This means that the benefits of tocilizumab will be underestimated (Luqmani et al. 2016)
Clinical assumptions	A relapse/flare can occur at any time after diagnosis	Andersson et al reported relapses/flares can occur regardless of time after diagnosis (when withdrawal of treatment is attempted). (Andersson, Malmvall, and Bengtsson 1986) BSR guidelines (Dasgupta 2010) state that the majority of early relapses occur due to rapid glucocorticoid tapering. (Dasgupta et al. 2010)
	The GC tapering regimen within the GiACTA trial is sufficiently representative of clinical practice not to have a major impact on cost-effectiveness	The fastest GC tapering regimen recommended in the BSR Guidelines is 52 weeks, if no relapse/flare occurs (Dasgupta et al. 2010)
	The duration of treatment with tocilizumab is not expected to exceed 24 months for the majority of patients	The benefits of continuous tocilizumab treatment beyond 12 months are not known from currently available data. However, the NICE scope considered current GCA treatment duration would be 18 – 24 months, so this suggests tocilizumab treatment duration would correspond to this range
	Increased GC dose due to flare is only for 7 days	Based on conservative modelling approaches
	The benefits of tocilizumab are continuous	Currently available open-label extension data from GiACTA show only ~50% of patients relapse/flare after withdrawing tocilizumab (cross-ref OLE data) (see B.2.6.6 Longer term disease control)

	The impact of flare on quality of life lasts 28 days	Based on market research, performed independently from Roche with respondents from a range of clinical specialities. The BSR guidelines and Royal College of Physicians report that standard treatment with GCs should continue for 4 weeks, or longer if symptoms continue. This suggests that symptoms of flare continue for at least 4 weeks (Dasgupta and GCA Guideline Development 2010) Also, flare duration in a published SLR of GCA reported that clinical improvement can take 2-4 weeks after treatment (Buttgereit et al. 2016)
	The management of GCA reported from the market research is representative of practice in England	This market research was performed independently from Roche with respondents from a range of clinical specialities
	GCA mortality is only increased indirectly, due to death from major strokes	Published systematic review and meta-analysis concluded that there was no long-term increase in mortality among GCA patients ((Hill et al. 2017))
	40% of strokes are minor, 60% are major	As reported in (Luqmani et al. 2016)
	The patient population included within the clinical trial is generalisable to clinical practice	The patients enrolled in GiACTA (see B.2.3.2 Baseline characteristics) closely represent the real-world GCA population according to evidence from the US MarketScan database and the UK Clinical Practice Research Datalink (CPRD), which show similar patient demographics (Petri et al. 2015; Broder et al. 2016)
Transitions	The different transition probabilities for time to first flare and time to subsequent flare measured between the tocilizumab and placebo arms during the GiACTA trial are maintained during the model extrapolation	Based on GiACTA data

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The absolute and incremental, discounted cost-effectiveness results are presented in Table 49, comparing tocilizumab treatment with GC versus GC alone. Table 50 also presents the discounted cost-effectiveness results for tocilizumab and GC treatment, but here with the tocilizumab PAS.

Table 49: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Prednisone alone	[redacted]	12.44	7.95	[redacted]	0.01	0.77	[redacted]
Tocilizumab with prednisone	[redacted]	12.45	8.71				

Table 50: Deterministic base-case results with the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Prednisone alone	[redacted]	12.44	7.95	£10,970.17	0.01	0.77	£14,336
Tocilizumab with prednisone	[redacted]	12.45	8.71				

B.3.8 Sensitivity analyses

B.2.8.1 Probabilistic sensitivity analysis

All model variables that had an assigned distribution are presented in Table 47. Uncertainty was characterised by standard error (if available), covariance matrix or by assuming an error of 20% from the mean if statistical uncertainty was not available from the data source. Drug acquisition costs were fixed.

A probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations to determine the uncertainty surrounding the base case ICERs. The scatter plots and the corresponding cost-effectiveness acceptability curves (with and without PAS applied) are shown in Figure 20, Figure 21, Figure 22, Figure 23. The range of uncertainty is consistent across variables considered, and are all beneath the cost-effectiveness threshold of £20,000 - £30,000/QALY.

Figure 20: Incremental cost and QALY base case results

Figure 21: Incremental cost and QALY base case results with PAS

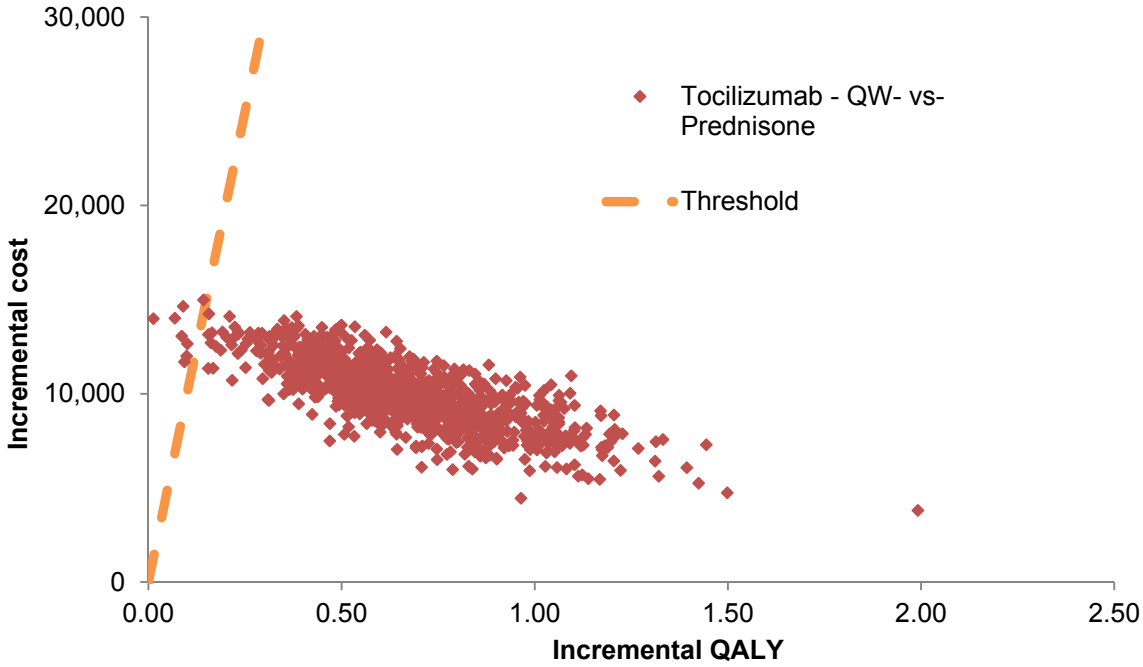
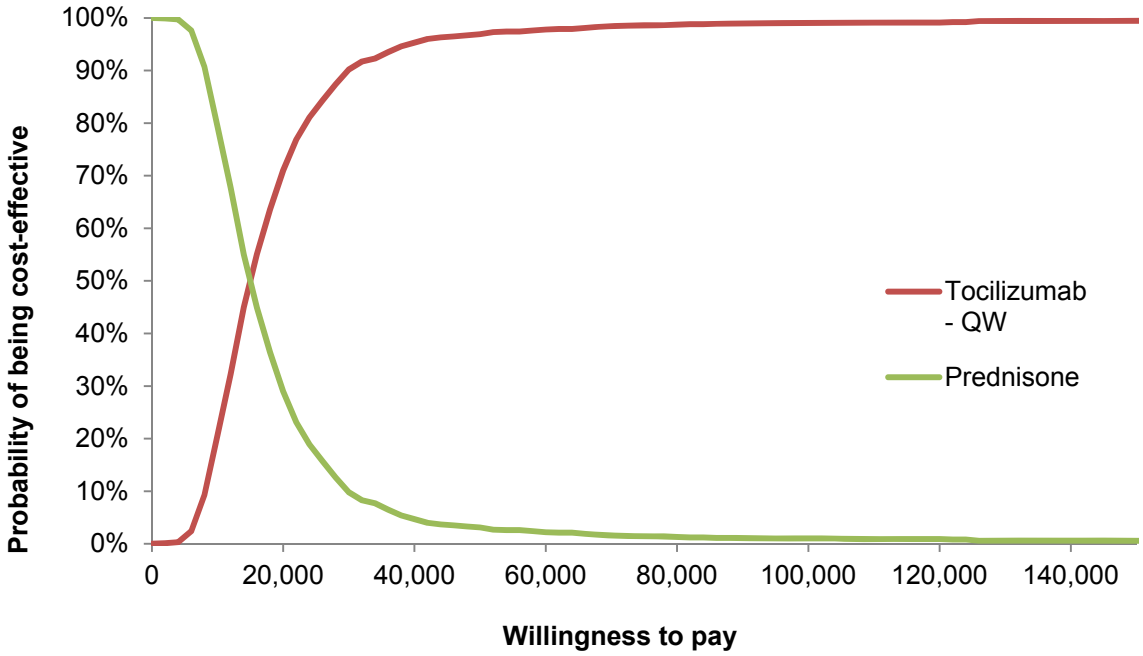


Figure 22: Cost-effectiveness acceptability curve

[redacted]

Figure 23: Cost-effectiveness acceptability curve with PAS



The probabilistic base case ICER was [redacted] (£14,335/QALY with PAS), comparable to the deterministic base case ICER. The PSA demonstrated that tocilizumab was more cost-effective in [redacted] of simulations (90% with PAS), at a threshold of £30,000/QALY gained.

The results from the deterministic and the probabilistic sensitivity analyses are comparable in their result that tocilizumab with GC is more cost-effective to treat GCA than GCs alone.

B.3.8.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis is presented in Table 51 and Table 52. The output variables have varied within around 5% - 10% above and below the base case value, subject to the influence of each variable on the ICER.

The results of the deterministic sensitivity analysis are shown in the tornado diagrams in Figure 24 and Figure 25.

Table 51: Deterministic sensitivity analysis

Parameter modified		Lower value	Lower ICER	Upper value	Upper ICER
Base case	Base case	Base case	[redacted]	Base case	[redacted]
Utility on remission	0.7713	0.75	[redacted]	0.80	[redacted]
Utility on flare	0.6420	0.63	[redacted]	0.66	[redacted]
Utility decrement on vision loss	-0.3673	-0.34	[redacted]	-0.39	[redacted]
Utility decrement on minor stroke	-0.1788	-0.15	[redacted]	-0.20	[redacted]
Utility decrement on major stroke	-0.4912	-0.45	[redacted]	-0.54	[redacted]
Rate of blindness from flare	0.0002	0.0001	[redacted]	0.0003	[redacted]
Rate of minor stroke from flare	0.0003	0.0002	[redacted]	0.0004	[redacted]
Rate of major stroke from flare	0.0002	0.0001	[redacted]	0.0003	[redacted]
Cost of fracture	1624.09	1,400.00	[redacted]	1,900.00	[redacted]
Cost of diabetes	48.2957	30.00	[redacted]	80.00	[redacted]
Cost of flare	259.7653	220.00	[redacted]	300.00	[redacted]
Cost of blindness year 1	97.5496	80.00	[redacted]	120.00	[redacted]
Cost of blindness year 2	93.9658	91.0000	[redacted]	96.0000	[redacted]
Cost of stroke	112.6899	105.0000	[redacted]	120.0000	[redacted]
Subsequent flare probability TCZ	0.0106	0.010	[redacted]	0.011	[redacted]
Subsequent flare probability PBO	0.0228	0.0210	[redacted]	0.0245	[redacted]

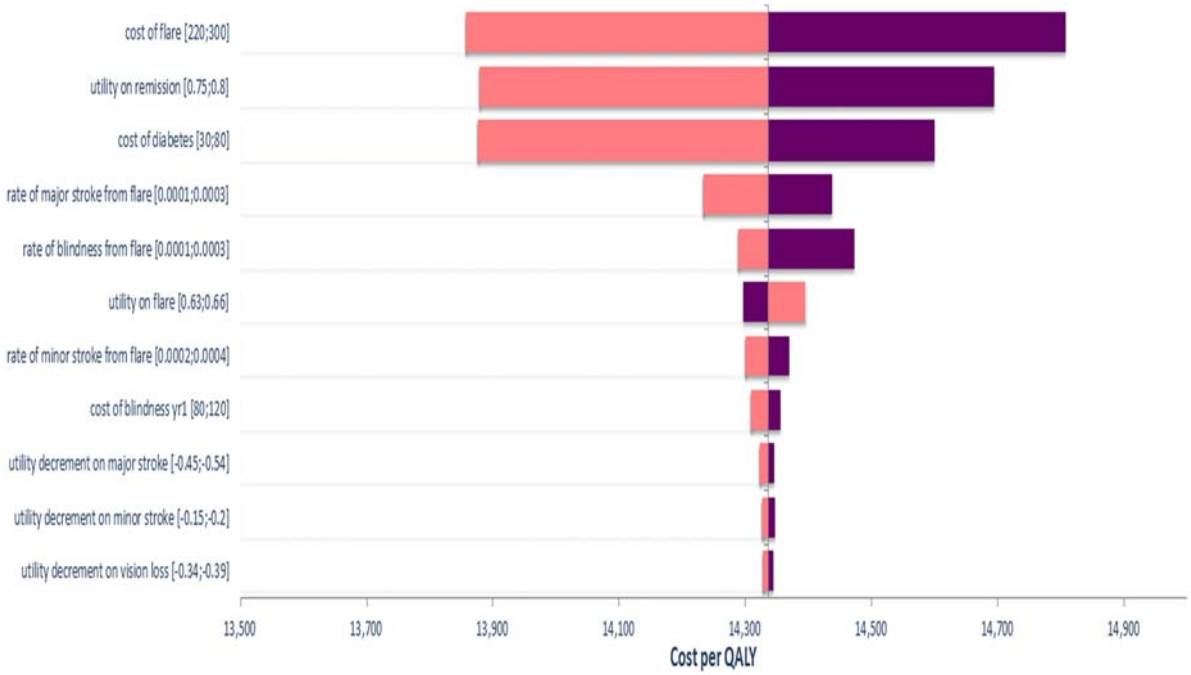
Table 52: Deterministic sensitivity analysis with PAS

Parameter modified	Base case values	Lower value	Lower ICER	Upper value	Upper ICER
Base case	Base case	Base case	£14,335.74	Base case	£14,335.74
Utility on remission	0.7713	0.75	£14,694.39	0.80	£13,879.29
Utility on flare	0.6420	0.63	£14,296.72	0.66	£14,394.66
Utility decrement on vision loss	-0.3673	-0.34	£14,344.39	-0.39	£14,328.57
Utility decrement on minor stroke	-0.1788	-0.15	£14,346.69	-0.20	£14,327.71
Utility decrement on major stroke	-0.4912	-0.45	£14,346.18	-0.54	£14,323.41
Rate of blindness from flare	0.0002	0.0001	£14,473.16	0.0003	£14,289.15
Rate of minor stroke from flare	0.0003	0.0002	£14,369.92	0.0004	£14,300.90
Rate of major stroke from flare	0.0002	0.0001	£14,437.67	0.0003	£14,234.08
Cost of fracture	1624.09	1,400.00	£14,336.63	1,900.00	£14,334.65
Cost of diabetes	48.2957	30.00	£14,600.70	80.00	£13,876.59
Cost of flare	259.7653	220.00	£14,807.59	300.00	£13,858.31
Cost of blindness year 1	97.5496	80.00	£14,355.75	120.00	£14,310.14
Cost of blindness year 2	93.9658	91.0000	£14,335.77	96.0000	£14,335.72
Cost of stroke	112.6899	105.0000	£14,338.95	120.0000	£14,332.69
Subsequent flare probability TCZ	0.0106	0.010	£13,992.57	0.011	£14,567.70
Subsequent flare probability PBO	0.0228	0.0210	£15,943.15	0.0245	£13,042.84

Figure 24: Tornado diagram showing the deterministic analysis for the base case

[redacted]

Figure 25: Tornado diagram showing the deterministic analysis for the base case with PAS



B.3.8.3 Scenario analysis

Different scenario analyses have been performed on the base-case and are illustrated in Table 53 and Table 54. These scenarios assessed different parametric models for the time to first flare, the extrapolation of the time to first flare result, and different stopping rules in the administration of tocilizumab.

In the parametric models, where a parametric tail is applied after the Kaplan-Meier curves, the time point is the follow up of the trial: 12 months. For the piecewise exponential, the cut-off point is the end time of GC tapering: 26 weeks and 52 weeks for the tocilizumab and GC arms, respectively.

A stopping rules for tocilizumab treatment were considered, where patients cease treatment after a fixed period of time, assuming though that the GCA control effect will be maintained. However, validating these stopping rules will require a longer follow-up of clinical data in GCA patients treated with tocilizumab, to be sure these assumptions are plausible in clinical practice and clinically meaningful for patients.

Table 55 and **Table 56** present additional scenario analysis that are of relevance to this appraisal, considering the clinical validity and sensitivity of the inputs chosen for the base case.

Table 53: Summary of different scenario analysis

Scenario	Value	ICER (£/QALY Gained)
Distribution Time to First Flare for tocilizumab	Exponential	[redacted]
	Weibull – base case	[redacted]
	Log-normal	[redacted]
	Gamma	[redacted]
	Log-logistic	[redacted]
	KM with Exponential tail	[redacted]
	KM with Weibull tail	[redacted]
	KM with Log-normal tail	[redacted]
	KM with Gamma tail	[redacted]
	KM with Log-logistic tail	[redacted]
Distribution Time to First Flare for GC	Exponential - base case	[redacted]
	Weibull	[redacted]
	Log-normal	[redacted]
	Gamma	[redacted]
	Log-logistic	[redacted]
	KM with Exponential tail	[redacted]
	KM with Weibull tail	[redacted]
	KM with Log-normal tail	[redacted]
	KM with Gamma tail	[redacted]
	KM with Log-logistic tail	[redacted]
Fixed duration of tocilizumab treatment (months)	12	[redacted]
	24 – base case	[redacted]
	36	[redacted]
	48	[redacted]
	60	[redacted]

Table 54: Summary of different scenario analysis with PAS

Scenario	Value	ICER (£/QALY Gained)
Distribution Time to First Flare for tocilizumab	Exponential	£21,260.97
	Weibull – base case	£14,335.74
	Log-normal	£9,490.30
	Gamma	£11,711.95
	Log-logistic	£11,270.53
	KM with Exponential tail	£21,061.10
	KM with Weibulll tail	£14,283.30
	KM with Log-normal tail	£9,515.06
	KM with Gamma tail	£11,683.98
	KM with Log-logistic tail	£11,239.18
Distribution Time to First Flare for GC	Exponential - base case	£14,335.74
	Weibull	£13,901.77
	Log-normal	£15,316.79
	Gamma	£15,394.65
	Log-logistic	£15,372.39
	KM with Exponential tail	£14,254.19
	KM with Weibulll tail	£13,897.16
	KM with Log-normal tail	£15,197.69
	KM with Gamma tail	£15,264.88
	KM with Log-logistic tail	£15,285.28
Fixed duration of tocilizumab treatment (months)	12	£2,792.28
	24 – base case	£14,335.74
	36	£25,308.89
	48	£35,719.62
	60	£45,574.70

Table 55: Scenarios analysis of relevance to the appraisal of tocilizumab in GCA

Parameter	Value	ICER (£/QALY)	Justification
Basecase		[redacted]	B.3.2.2. Model structure
Time horizon	20 years	[redacted]	Standard variable
Age patient age	73 years	[redacted]	(Wilson et al. 2017a)
Annual reduction in re-flare rate	5% 10%	[redacted]	Published literature vary greatly on the expected re-flare rate in GCA patients (Labarca et al. 2016) (Alba et al. 2014)
Mean GC cumulative dose	14 g	[redacted]	CPRD mean dose may be underestimating due to lack of rheumatologist prescriptions
Discount rate: costs	1.5%	[redacted]	Varying assumptions behind the NICE reference case
Discount rate: utilities	1.5%	[redacted]	
Discount rate: both costs and utilities	1.5%	[redacted]	

Table 56: Scenarios analysis of relevance to the appraisal of tocilizumab in GCA with PAS

Parameter	Value	ICER (£/QALY)	Justification
Basecase		£14,336	B.3.2.2. Model structure
Time horizon	20 years	£15,345	Standard variable
Age patient age	73 years	£17,163	(Wilson et al. 2017a)
Probability of subsequent flare (Annual reduction in re-flare rate)	5% 10%	£18,889 £22,740	Published literature vary greatly on the expected re-flare rate in GCA patients (Labarca et al. 2016) (Alba et al. 2014)
Mean GC cumulative dose	14 g	£13,037	CPRD mean dose may be underestimating due to lack of rheumatologist prescriptions
Discount rate: costs	1.5%	£13,384	Varying assumptions behind the NICE reference case
Discount rate: utilities	1.5%	£12,337	
Discount rate: both costs and utilities	1.5%	£11,518	

B.3.8.4 Summary of sensitivity analyses results

Extensive deterministic sensitivity analyses were conducted by varying individual parameters, using the 10th and 90th percentile from the probabilistic distribution simulation as lower and upper values, respectively. In addition, sensitivity of the results were tested by using alternative utilities, alternative assumptions for time to first flare, and extrapolation functions.

The ICERs remained close to the base-case value in most cases. The ICER was most sensitive for the following inputs:

Duration of tocilizumab treatment

Tocilizumab treatment duration is the biggest driver of cost-effectiveness in this model. It has been widely published that GCA is a condition that has an acute phase, which may be followed by remission or by relapse, but it is understood that a proportion of patients do not require continuous treatment for the duration of their life. Given this uncertain aetiology, the uncertainty of the tocilizumab treatment duration is inevitable. Ranging from [redacted] (with PAS £2,792) for 1 years treatment with tocilizumab to [redacted] (with PAS £45,574.70) for 5 years tocilizumab treatment.

Probability of subsequent flare

Related to the above uncertainty regarding the aetiology of GCA; the annual reduction in flare rate for patients on only GC, or patients receiving tocilizumab plus GC substantially impacts the ICER calculations. The ICER increased to [redacted] (£18,889 with PAS) with a 5% reduction in annual re-flare rates, and to [redacted] (with PAS £22,740) with a 10% reduction in annual re-flare rates. (Labarca et al. 2016) (Alba et al. 2014)

B.3.9 Subgroup analysis

Newly diagnosed GCA patients are those who have not yet received treatment, while relapse/refractory patients have received GC treatment and either not responded (refractory) or responded but their GCA has relapsed/flared again (relapsed).

The NICE scope and decision problem stated two patient subgroups were important: newly diagnosed, and relapsed/refractory. Both of these subgroups were defined *a priori* in the GiACTA trial. (Tuckwell et al. 2016; Stone et al. 2017) However, since the overall ITT population is cost-effective, and there is no difference in efficacy between the two subgroups a further analysis of cost-effectiveness is not considered here. Furthermore, these subgroup

analyses would not be statistically powered, whilst the ITT data are. Lastly, the real world data used to support extrapolation of effects reported during the GiACTA trial are not distinguished by subgroup, but are only available for the GCA population – hence greater uncertainty would be introduced here.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

NICE Scientific Advice was sought by Roche for the GCA indication for tocilizumab, and the advice was incorporated into the clinical development: specifically the inclusion of a control arm with GC tapering that better matched UK clinical practice – 52 weeks taper in addition to the 26 weeks. Also, this allowed disease aspects to be captured from a health economic perspective.

The *de novo* model structure was developed by Roche; however, during development it was reviewed by independent, external clinical and health economic experts to ensure robust face validity as well as having appropriate and robust clinical assumptions.

In addition to validating the model concept, the model inputs were validated were possible via published literature or robust real world data analysis, including the CPRD analysis of GCA and matched GC-receiving, non-GCA patients (Wilson et al. 2017g) plus an extensive, third-party, market research of practicing UK clinicians (n=121) .

Moreover, an independent, external agency quality checked the technical aspects of the model for validity and consistency. This technical validation comprised the following areas:

- Checking for technical programming or calculation errors (this includes the VBA coding)
- Looking for logical errors or common sense issues related to the model structure, assumptions, data inputs, results and graphical representations.

Key model outputs were also validated by clinical opinion, including the re-flare rate and the proportion of patients on maintenance therapy (B.1.3.7 External expert input).

B.3.11 Interpretation and conclusions of economic evidence

The cost-effectiveness model extrapolates the clinical benefit of tocilizumab with GC combination therapy versus GC monotherapy, and demonstrates superiority in controlling GCA relapses/flares, a longer period of sustained remission, and clinically meaningful and statistically significant steroid-sparing. This results in an improved QoL due for patients which is cost-effective, while avoiding GCA-related complications and GC-related AEs.

The full (ITT) population cost-effectiveness analysis presented is the most relevant to the UK population, and also best matches the NICE scope and decision problem, plus the wording of the CHMP Positive Opinion ahead of Marketing Authorisation. The cost inputs selected to populate the model are the most relevant to NICE, as requested in the reference case. Additionally, the utility benefit reported from the GiACTA trial was measured with the EQ-5D, which also matches NICE reference case.

As with all *de novo* cost-effectiveness models in relatively rare diseases, there are a range of strengths and weaknesses for this analysis, including the following:

- The model extrapolates 52 weeks of clinical data over a 30 year horizon to model the lifetime costs and benefits of using tocilizumab in clinical practice. This is important when considering the re-flare rate beyond the GiACTA trial, and particularly the difference in re-flare rate between tocilizumab treated patients and GC patients;

- Since tocilizumab is not used routinely in clinical practice and the aetiology of GCA varies between patients it is not certain how long to model tocilizumab treatment for, which substantially impacts the cost-effectiveness analysis for GCA;

- Additionally, it is unclear what tocilizumab re-treatment rules are optimal in GCA, both clinically and for cost-effectiveness;

- The use of a 52 week steroid tapering regimen within the GiACTA trial which is at the lower end of the regimens used in UK clinical practice.

- Inability to include all of the impacts of GC upon patients during to lack of evidence meaning that the benefits of steroid sparing through use of tocilizumab are underestimated.

- The main strengths of the cost-effectiveness evaluation presented here is that GiACTA is this the largest RCT of GCA patients, plus the extrapolations are supported by non-RCT data, to inform the clinically uncertain parameters that are

important for the cost-effectiveness modelling. These include, the substantial market research of UK clinicians treating GCA patients (Research Partnerships 2017) and the CPRD analysis (Wilson et al. 2017g).

Further analysis to improve the certainty of the cost-effectiveness analysis

Interim analysis data from the open label extension of the GiACTA trial would improve the cost-effectiveness analysis, as this would help to better inform the assumptions around the aetiology of GCA on GC-only treatment, plus also the extrapolation of longer term outcomes after the 52 week GiACTA duration.

Furthermore, better clinical characterisation of the duration and QoL impact of a relapse/flare would also increase the certainty within the cost-effectiveness modelling.

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Single technology appraisal

Tocilizumab for treating giant cell arteritis [ID1051]

Dear [redacted]

The Evidence Review Group, Centre for Reviews and Dissemination York and the technical team at NICE have looked at the submission received on 10 August 2017 from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **15 September 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (ross.dent@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Epidemiology

A1. Page 17 of the company submission gives the UK incidence of giant cell arteritis in people over 40 years old. As it is mainly a condition of people aged over 50 years and most common in those over 70 years, please provide estimates of the incidence in these age groups.

GiACTA trial

A2. Please confirm how many patients in each treatment arm were from the UK.

A3. Eight patients withdrew from the study because of a lack of efficacy. Please provide further details on the reasons why instead of receiving escape therapy, these patients withdrew from the trial.

A4. Loss of vision is described in the submission as an important adverse outcome of giant cell arteritis. However, it is not included in the baseline characteristics listed for the GiACTA trial in Table 7 of the submission. Please provide details of vision loss at baseline.

A5. Vision loss is not recorded as an outcome in GiACTA. Does the lack of this outcome mean that the population in the GiACTA trial is at the mild end of the disease spectrum?

A6. Please clarify the patient pathway through the trial: our understanding is that if a patient randomised to tocilizumab has not achieved remission by week 12 or their disease flares, they stay in the trial and continue with tocilizumab treatment for the full 52 weeks but are counted as non-responders. If this is correct, please comment on how reflective this is likely to be of clinical practice.

A7. Table 18 in the GiACTA clinical study report presents the individual components of (or lack of) sustained remission, but does not present the number who did not achieve remission at week 12. Please provide this.

A8. In the analysis of time to first flare, the definition given is ‘time to flare after remission’. We interpret this to mean that patients who do not achieve remission are never at risk of flare, and patients are only at risk of flare from the time they achieve remission.

a. The analysis presented in Figure 3 and Table 12 of the submission states that patients who were never in remission were censored at Day 1. However the curves

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presented in Figure 3 would suggest that was almost never the case: is it correct that almost all patients were in remission at week 0?

b. Please clarify whether 'never achieved remission' means up to week 12 (as for the primary outcome), or whether remission could have been at any point up to week 52.

c. Unless all patients who achieved remission did so before or at week 0, the time of remission is not accounted for in the analysis. Please provide:

- The number of patients (by treatment arm) who never achieved remission.
- The number of patients (by treatment arm) who achieved remission at or before week 0.
- Please list (by treatment arm) those patients who achieved remission after week 0 and the time to remission.
- Unless no patient achieved remission after week 0, please rerun the analysis using time zero as the time when remission was achieved. Please provide the numbers at risk of flare at each time point and also the median duration of follow-up whilst at risk of flare.

d. The Stone et al. (2017) publication states that patients who never had remission were considered to have had a flare at week 0. Was this the case for all presentations of this analysis or were these patients censored as stated in the submission and GiACTA clinical study report?

A9. Please provide details of how many patients in each trial arm completed the health-related quality-of-life questionnaires (PGA, SF-36, FACIT-fatigue and EQ-5D) at each assessment time point. Please clarify the reasons for incomplete capture of this information such as loss to follow-up or exclusion of patients for specific reasons (e.g. use of escape therapy).

GiACTA Part 2

A10. Figure 7 on page 54 of the submission presents the patient disposition in part 2 of GiACTA by response. Please split the non-responder branch by new onset/relapsed disease to match the responder branch.

A11. On page 56 of the submission it states that, "[redacted]."

Please provide the actual figures behind this statement. In addition please provide the baseline (i.e. at the start of Part 1) disease status (newly diagnosed or relapsing) for each row of Tables 19 and 20.

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Section B: Clarification on cost-effectiveness data

B1. **Priority question:** There appears to be an error in the calculation of QALYs. This relates to 2 aspects; (i) the length of time patients experience a lower utility value as the result of a flare; and (ii) the proportion of patients who are in subsequent remission (not experiencing a flare). These issues are described in turn below:

(i) Patients who have a flare move to the flare state for 1 cycle (1 week) and receive the utility value associated with this state. However, these patients are excluded from the remission state for 4 weeks in the QALY calculation (column BC in sheet "TCZ (QW) arm" and column BB In sheet "CS (52Wk) arm"). This means that these patients appear to spend 3 weeks accruing no health-related quality-of-life.

(ii) When calculating QALYs 'on Remission', the proportion of patients in subsequent remission (second component of formulae in column BC in sheet "TCZ (QW) arm" and BB in sheet "CS (52Wk) arm") is estimated as being the proportion of patients in the "Subsequent Remission (on escape steroid regiment)" state minus the proportion in the "Cumulative flare 4 weeks (for disutility)" column. This approach can result in negative QALYs for the second component of the formulae for QALYs 'on Remission' (i.e. a negative proportion of patients in subsequent remission). .

Please correct these errors and submit a revised Excel model. Please also provide a description of the corrections to the model, together with a complete set of corrected results.

For clarification questions: B2-B3, please report the results based on the corrected model.

B2. **Priority question**: Please provide tables similar to Tables 49 and 50 in the submission for the probabilistic base-case results for the intention-to-treat population.

B3. **Priority question**: As requested in the NICE scope, please provide additional analyses and results for the following subgroups: (i) New-onset giant cell arteritis and (ii) Relapsing giant cell arteritis. The relevant input data for these subgroups appears to be already included within the 'Parameters-SAS outputs NPH' sheet. Specifically, please provide for each subgroup:

a. Base-case result tables (deterministic and probabilistic).

b. Figures of the scatter plots and cost-effectiveness acceptability curves.

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c. Revised figures (Figs 10, 11) and tables (Table 34) for time to first flare transition probability

d. Revised table (Table 35) for the transition probability to subsequent flares

B4. **Priority question**: Please incorporate additional functionality in the revised Excel model to allow the user to select the following populations and associated parameter inputs: (i) Intention-to-treat; (ii) New-onset and (iiii) Relapsing.

B5. **Priority question:** The model potentially double counts costs during a flare episode. The model appears to attribute a 3-month flare cost at the point of a flare (i.e. during a specific cycle of 1 week duration). However, for the next 11 weeks these patients still appear to receive other management costs as well. Please confirm whether our understanding is correct and provide further justification for the assumptions.

B6. **Priority question**: There are several aspects of the model which require further clarification in relation to external validity. In particular:

a. The mean number of flares (19.67) predicted over a 30-year period appears high for the glucocoticosteroids alone comparator. Proven et al (2003) reported a maximum of 7 flares in any patient based on a median follow-up of 10-years compared with the current model predictions of 10.35 relapses over the same period (i.e. over 1 relapse/year). Similarly, Larbaca et al (2015) reported a median relapse rate of 0.4 relapses/year (IQR 0.21-0.64) over a median duration of 5-years (i.e. approximately 2 relapses over 5 years compared with the current model predictions of 5.26 over the same period).

<u>Please provide further clarification on the validation undertaken and any additional evidence to support the external validity of the predicted number of flares.</u>

b. It is also unclear whether patients who are reported in 'flare at visit' during consecutive follow-up times (e.g. at weeks 44 and 48) are being treated as multiple or single counts in estimating the time to subsequent flare transition probability. If consecutive periods of flare are being treated as multiple counts, please present an additional sensitivity analysis based on re-estimating the weekly probability of flare assuming that flares reported over consecutive follow up periods are treated as a single flare episode.

c. The selected parametric distribution (exponential) for the prednisone strategy predicts that less than 2% of patients receiving glucocorticosteroids will not have experienced a first flare by 5 years. Several longitudinal cohort studies with follow-up data beyond 5 years (e.g. Proven 2003, Alba 2014, Larbaca 2015, Restuccia 2016) report a significantly higher proportion of patients

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receiving glucocorticosteroids that have not experienced a flare by 5 years (approximate range 30-50% across studies). Furthermore, these studies also appear to suggest that the hazard of relapse/recurrence tends to decrease during long-term follow-up, suggesting reduced disease activity over time (Cid and Alba, 2015).

Please provide further justification to support the selected parametric distribution and any additional evidence to support the external validity of the longer term predictions.

B7. **Priority question**: A key feature of the base-case analysis is the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration. This is justified in Table 31 on the basis that "early results from the OLE (open label extension study) suggest that very few patients re-flare after treatment with tocilizumab". However, Table 48 (and data reported in section B2.6.6) later state that "50% of patients relapsed/flared after withdrawing tocilizumab therapy". This figure appears similar to that reported by Adler et al (2016) following cessation of tocilizumab in the previous RCT, where the authors concluded that "clinical and serologic remission in response to TCZ (tocilizumab) for 52 weeks does not result in relapse-free survival after termination of treatment".

a. Please provide further justification to support the appropriateness and validity of this key assumption.

b. Please present further justification for why data reported in either or both the open label extension study and/or Adler et al (2016) studies were not formally used.

B8. Please provide the full report for the market research reference (Research Partnerships 2017).

B9. **Priority question**: The risk of giant cell arteritis related complications (loss of vision and stroke) assumes a surrogate relationship between these and relapse/flare events and that these risks are modifiable with treatment with tocilizumab. Please provide further justification and/or references to support these assumptions.

B10. **Priority question**: Our understanding is that patients in England and Wales would be likely to be treated with prednisolone rather than prednisone. The current price of prednisolone (5mg, 28 tablets = £0.81) is lower than that assumed for prednisone (5mg, 30 tablets = £26.70). Please provide further justification for assuming the cost of oral prednisone rather than prednisolone and present an additional scenario assuming the lower acquisition cost of prednisolone.

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B11. **Priority question**: The GiACTA clinical study report (page 47) states that the first 4 subcutaneous injections of tocilizumab required administration in a setting where medications and resuscitation facilities were available and patients were required to stay for 2 hours following each injection. It also states that patients and caregivers were trained to perform the subcutaneous injections at their first visit and that clinical staff could administer the injections if a patient was unable or unwilling to self-administer. Please provide:

a. Clarification on whether patients would require administration of their initial injections in a health care facility in routine clinical practice and any associated resource use and cost implications for the NHS.

b. An estimate of the resource and costs required to train and support a patient and/or carer to self-administer tocilizumab.

c. The proportion of patients in GiACTA who were unable to or unwilling to self-administer tocilizumab and discuss any associated resource and cost implications for the NHS.

B12. Please provide further details on the data from the Market Scan database used to inform the cumulative glucocorticosterois dose equation parameters.

B13. **Priority question**: The EQ-5D analyses reported in Tables 15 and Figure 5 of the submission exclude post-escape EQ-5D data (GiACTA clinical study report, page 533). Please provide results including post-escape data based on the repeated measures model used for other endpoints, including the same covariates and interactions: treatment, starting prednisone dose (<=30mg/day, >30mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction.

B14. **Priority question**: Please provide additional clarification on the specification and output of the mixed model used to inform health state utilities. Please also clarify: (i) how the analysis addresses the mismatch between the 4-week duration of flare and the frequency of the planned EQ-5D assessments and (ii) why subsequent flares were excluded and any implications this has for the analysis.

B15. Please provide further clarification on Tables 43 and 44 in the submission. It is unclear how the data in these tables relate to the specific health states.

B16. In Table 47 (summary of model variables in base case), please clarify what the variables “treatment in primary care only” and “primary care referral to specialist care” represent and how these relate to the health states and/or assumptions of the model.

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Section C: Textual clarifications and additional points

C1. The PRISMA flow diagram on page 43 and the description of the search results on page 42 of the Appendix refers to, *"Literature database searches yielded 1,014 records. Additionally, two records were identified and included through other sources."* However, there is no description of what these other sources were, and how the 2 records were identified. Please provide these details.

References

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Contents

Tables

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Introduction

The GiACTA trial was the largest RCT conducted to date in GCA patients, so represents the best available clinical evidence to inform decision making. Some limitations existed however, including the lack of a standardised definition of flare/relapse among the GCA clinical community. Related to this, relapsed/refractory patients have not been modelled separately here, as again the definitions of these are not standardised. It's seems important to note, that the clinical community have stated then even considering GCA patients as being newly diagnosed or relapsed/refractory is not a common approach to treatment decisions.

Section A: Clarification on effectiveness data

Epidemiology

A1.

Page 17 of the company submission gives the UK incidence of giant cell arteritis in people over 40 years old. As it is mainly a condition of people aged over 50 years and most common in those over 70 years, please provide estimates of the incidence in these age groups.

Response

Smeeth et al (2006) investigated factors affecting incidence of diagnosis of polymyalgia rheumatica (PMR) and temporal arteritis (TA) in the UK. (Smeeth, Cook, and Hall 2006) They reported rates of diagnosis of TA broken down by age group. Rates of diagnosis of TA in patients 70-79 years was given as 5.9 per 10,000 person-years with a female: male incidence rate ratio of 2.1. Rates of diagnosis of TA in patients 80+ years was given as 6.0 per 100,000 person-years with a female: male incidence rate ratio of 1.5 (see Table 3 in the publication).

Petri et al (2015) investigated the incidence of GCA using data from the UK Clinical Practice Research Datalink. (Petri et al. 2015) They reported that incidence in women ages 70–79 years was 7.4 per 10,000 person-years. They also estimated the age-adjusted female/male incidence ratio at 1.99. (This provides an estimate of incidence in men aged 70-79 years as ~3.7 per 10,000 person-years - see figure 1 in the publication). The authors reported that incidence rate peaked in the 70-79 years age group; rates decline for patients aged 80+ years (see figure 1 in the publication; actual rates not provided, but estimates from the graph

may be given at ~6 per 100,000 person-years for females and ~4 per 100,000 person-years for males).

GiACTA trial

A2.

Please confirm how many patients in each treatment arm were from the UK.

Response

There were 11 recruiting centres in the UK, recruiting 16 patients between them:

- 3 patients in the PBO QW + 26-week GC taper arm
- 2 patients in the PBO QW + 52-week GC taper arm
- 7 patients in the TCZ QW + 26-week GC taper arm
- 4 patients in the TCZ Q2W + 26-week GC taper arm

One patient (in the TCZ Q2W arm) was randomised but did not receive study drug. The remaining 15 patients were in the ITT population.

A3.

Eight patients withdrew from the study because of a lack of efficacy. Please provide further details on the reasons why instead of receiving escape therapy, these patients withdrew from the trial.

Response

When a patient withdrew from the study, the investigator completed the study discontinuation page of the Case Report Form (CRF), selecting the reason as 'lack of efficacy'. There was no requirement or option when 'lack of efficacy' was selected to specify whether the patient received escape therapy (requirement for further specification of results was only needed for 'non-compliance', 'physician decision' or 'other').

Of the eight patients who withdrew from the study due to lack of efficacy, the majority of these patients withdrew despite having receiving escape steroids because their physician wanted to put them on alternative therapy which was not permitted per protocol (e.g.in most cases methotrexate):

- six experienced a GCA flare, received escape prednisone therapy and subsequently withdrew (two from PBO QW + 26-week GC taper arm; two from PBO QW + 52-week GC taper arm; two from TCZ Q2W + 26-week GC taper arm)

- two patients needed treatment with IV steroids which were not permitted per protocol and so were withdrawn from the study (one from TCZ QW + 26-week GC taper arm; one from TCZ Q2W + 26-week GC taper arm); one patient had highly active disease and needed IV steroids; in the other case the physician deemed IV steroids necessary (no additional details available).

A4.

Loss of vision is described in the submission as an important adverse outcome of giant cell arteritis. However, it is not included in the baseline characteristics listed for the GiACTA trial in Table 7 of the submission. Please provide details of vision loss at baseline.

Response

Table 12 of the CSR provides details of the baseline disease characteristics. Vision impairment was reported in a small number of patients at baseline: Blurred vision was reported for 14 patients (6%) with amaurosis fugax reported in 1 patient in each of the TCZ treatment groups. Unilateral blindness was reported in 1 patient in each treatment group and bilateral blindness was reported in a single patient in the TCZ Q2W group. Anterior arteritic ischemic optic neuropathy was reported in 1 patient in each of the TCZ treatment groups.

Furthermore, Table 11 of the CSR shows that 7-14% of patient had ischaemia-related vision loss at diagnosis. It is important to remember that patients had been treated with high-dose steroids prior to baseline, so their disease may have been less active at baseline compared with diagnosis.

Table 1: Extract from CSR Table 12 - Summary of GCA Disease Characteristics at Baseline (All Patients)

	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Baseline Bilateral Blindness				
Yes	0	0	0	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (98.0%)
Baseline Ischaemic Optic Neuropathy				
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)
Baseline Amaurosis Fugax				
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)
Baseline Blurred Vision				
Yes	2 (4.0%)	5 (9.8%)	4 (4.0%)	3 (6.0%)
No	48 (96.0%)	46 (90.2%)	96 (96.0%)	47 (94.0%)
Baseline Diplopia				
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
Baseline Unilateral Blindness				
Yes	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
No	49 (98.0%)	50 (98.0%)	99 (99.0%)	49 (98.0%)

A5.

Vision loss is not recorded as an outcome in GiACTA. Does the lack of this outcome mean that the population in the GiACTA trial is at the mild end of the disease spectrum?

Response

Vision loss was recorded as part of the clinical assessment for each patient at each study visit. Specifically, bilateral blindness, unilateral blindness, diplopia, blurred vision, amaurosis fugax, and ischaemic optic neuropathy were recorded. 7-14% of patients enrolled to GiACTA having ischemia-related vision loss at diagnosis (see CSR Table 11).

The observation of no new reports of permanent unilateral or bilateral vision loss during the trial is not reflective of a ‘mild’ disease population (see also the response to B9). The design of the GiACTA study emphasised the importance of patient safety by permitting ‘low hurdle’ triggering of escape prednisone therapy at the discretion of the investigator. Additionally, the level of clinical excellence employed by the investigators in monitoring disease activity ensured that any increase in disease activity was appropriately treated to prevent severe complications such as permanent vision loss. One patient who had been assigned to the TCZ Q2W arm had anterior ischemic optic neuropathy and vision loss that resolved after treatment with glucocorticoids.

In their publication on the baseline characteristics of patients in the GiACTA trial, Tuckwell et al noted “surprisingly high percentage of the patients enrolled (17% of the overall cohort) was classified as having disease refractory to glucocorticoids. These patients were judged by their physicians never to have been in remission, despite courses of glucocorticoids usually considered sufficient for remission induction.” They also concluded that “the GiACTA trial has enrolled a cohort of patients who are highly representative of the general GCA population in terms of demographic and clinical features.” (Tuckwell 2015)

Furthermore, 38-50% of patients had positive result by imaging studies indicating large vessel GCA (i.e. involvement of the aorta and its branches). Patients with large vessel disease are significantly younger, have longer duration of symptoms prior to diagnosis, and less likely to have visual loss. However, the risk of relapse is higher in patients with large vessel disease and they are likely to require high doses of steroids for long periods of time.

Finally, 88-95% of patients had a positive temporal artery biopsy (TAB) (see CSR Table 11). A positive TAB is associated with neuro-ophthalmic complications such as visual loss and cerebrovascular stroke. (Dasgupta et al. 2010)

A6.

Please clarify the patient pathway through the trial: our understanding is that if a patient randomised to tocilizumab has not achieved remission by week 12 or their disease flares, they stay in the trial and continue with tocilizumab treatment for the full 52 weeks but are counted as non-responders. If this is correct, please comment on how reflective this is likely to be of clinical practice.

Response

The assumption described in A6 is correct. Given that the tocilizumab GCA program used a single pivotal phase 3 trial, Roche elected to employ a high hurdle composite efficacy endpoint that centred around a requirement for a 40 week period of flare-free remission from week 12 through week 52 (with steroids discontinued by week 26) which, if met, would provide compelling evidence of the therapeutic benefit of tocilizumab in this disease.

In clinical practice, however, a patient who does not achieve remission within 12 weeks of tocilizumab initiation, or experiences an increase in disease activity that requires an upward adjustment of glucocorticoid therapy would not necessarily be considered by the treating physician as a treatment failure. The goal of therapy with tocilizumab in clinical practice will

be maintenance of disease control with much-reduced steroid exposure. This has been corroborated by discussion with clinicians with experience of using tocilizumab in GCA patients.

A7.

Table 18 in the GiACTA clinical study report presents the individual components of (or lack of) sustained remission, but does not present the number who did not achieve remission at week 12. Please provide this.

Response

The numbers and proportions of patients who were not in remission at week 12 and who were not eligible for sustained remission (up to week 52) at week 12 are shown in the table below:

Table 2: Patients remission status at Week 12

Week 12, n (%)	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Not in remission	7 (14.0)	9 (17.6)	7 (7.0)	6 (12.2)
Not eligible for sustained remission	29 (58.0)	26 (51.0)	17 (17.0)	9 (18.4)

A8.

In the analysis of time to first flare, the definition given is 'time to flare after remission'. We interpret this to mean that patients who do not achieve remission are never at risk of flare, and patients are only at risk of flare from the time they achieve remission.

a) *The analysis presented in Figure 3 and Table 12 of the submission states that patients who were never in remission were censored at Day 1. However the curves presented in Figure 3 would suggest that was almost never the case: is it correct that almost all patients were in remission at week 0?*

Response

Approximately 50-60% of patients in all groups were in remission at baseline (please refer to response to 8c for numbers). Only 7 patients were censored at Day 1 due to never being in remission (please refer to response to 8b below).

b) *Please clarify whether 'never achieved remission' means up to week 12 (as for the primary outcome), or whether remission could have been at any point up to week 52.*

Response

"Never achieved remission" means the patient never achieved remission throughout the entire study up to Week 52. Note that the time to flare endpoint is not dependent on the patient achieving remission at Week 52 as this was only a component for the primary endpoint of sustained remission.

c) *Unless all patients who achieved remission did so before or at week 0, the time of remission is not accounted for in the analysis. Please provide:*

- *The number of patients (by treatment arm) who never achieved remission.*
- *The number of patients (by treatment arm) who achieved remission at or before week 0.*
- *Please list (by treatment arm) those patients who achieved remission after week 0 and the time to remission.*
- *Unless no patient achieved remission after week 0, please rerun the analysis using time zero as the time when remission was achieved. Please provide the numbers at risk of flare at each time point and also the median duration of follow-up whilst at risk of flare.*

Response

- There were 7 patients who never achieved remission; 2 in each of the PBO QW +26, TCZ QW and TCZ Q2W groups, and 1 in the PBO QW+52 group.

- The number (proportion) of patients who were in remission at baseline (week 0) are as follows: 32 (64%) in PBO+26, 26 (51%) in PBO+52, 55 (55%) in TCZ QW and 29 (59%) in TCZ Q2W.

- Please see Table 3 for a listing of time to remission for patients not in remission at baseline, by treatment group. Note that patients who never achieved remission are included in the listing but have a missing remission time.

Table 3: Time to Remission for Subjects not in Remission at Baseline, ITT Population

PBO QW + 26 Week GC Taper (n=50)		PBO QW + 52 Week GC Taper (n=51)		TCZ QW + 26 Week GC Taper (n=100)		TCZ Q2W + 26 Week GC Taper (n=49)	
Patient	**Time to remission (days)**	**Patient**	**Time to remission (days)**	**Patient**	**Time to remission (days)**	**Patient**	**Time to remission (days)**
A1	28	B1	15	C1	22	D1	29
A2	86	B2	28	C2	8	D2	57
A3	8	B3	197	C3	22	D3	8
A4	23	B4	22	C4	8	D4	8
A5	8	B5	15	C5	9	D5	57
A6	9	B6	29	C6	8	D6	-
A7	8	B7	8	C7	-	D7	61
A8	8	B8	29	C8	8	D8	17
A9	107	B9	15	C9	15	D9	8
A10	8	B10	85	C10	9	D10	59
A11	8	B11	9	C11	30	D11	309
A12	-	B12	8	C12	11	D12	316
A13	8	B13	141	C13	8	D13	169
A14	8	B14	8	C14	8	D14	22
A15	-	B15	57	C15	-	D15	22
A16	85	B16	58	C16	8	D16	-
A17	8	B17	-	C17	33	D17	22
A18	7	B18	113	C18	8	D18	8
		B19	169	C19	8	D19	15
		B20	8	C20	8	D20	85
		B21	56	C21	8		
		B22	15	C22	86		
		B23	22	C23	8		
		B24	84	C24	8		
		B25	15	C25	8		
				C26	8		
				C27	9		
				C28	57		
				C29	142		
				C30	8		
				C31	6		
				C32	8		
				C33	15		
				C34	8		
				C35	6		
				C36	15		
				C37	7		
				C38	8		
				C39	8		
				C40	9		
				C41	29		
				C42	8		
				C43	12		
				C44	8		

- The current time to first flare analysis already uses time zero as the time when remission was first achieved post-baseline. The time to flare is calculated as the date of flare minus the date of first remission plus one day. The time to first flare analysis has been updated to also account for baseline remission so that patients in remission

at baseline will have a time 0 of baseline. An updated Kaplan-Meier plot and analysis summary are attached.

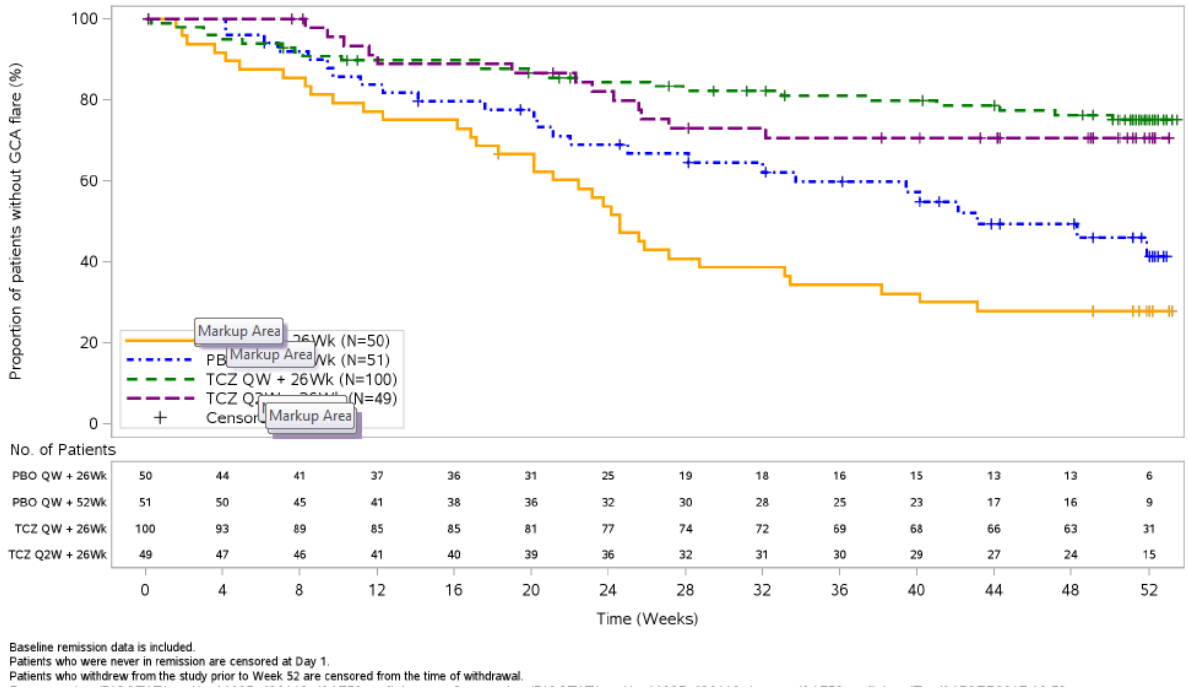
The number of patients at risk of flare at each time point is presented in Table 4 and can also be found in Figure 1, underneath the plot.

Table 4: Number of patients at risk of flare at each timepoint

Number at risk	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52
PBO+26	50	44	41	37	36	31	25	19	18	16	15	13	13	6
PBO+52	51	50	45	41	38	36	32	30	28	25	23	17	16	9
TCZ QW	100	93	89	85	85	81	77	74	72	69	68	66	63	31
TCZ Q2W	49	47	46	41	40	39	36	32	31	30	29	27	24	15

The median duration of follow-up whilst at risk of flare (i.e. time to flare or censoring) was 167.5 days (PBO+26), 236 days (PBO+52), 358 days (TCZ QW) and 310 days (TCZ Q2W).

Figure 1: Kaplan-Meier plot of time to first GCA disease flare following clinical remission, by treatment group, ITT population



d) *The Stone et al. (2017) publication states that patients who never had remission were considered to have had a flare at week 0. Was this the case for all presentations of this analysis or were these patients censored as stated in the submission and GiACTA clinical study report?*

Response

The wording in the footnote of the Stone et al publication was in-part slightly misleading. Patients who never achieved remission were censored at Week 0 and so were handled like a withdrawal patient rather than a flare patient. They were censored in this way for all time to flare analysis presentations.

A9.

Please provide details of how many patients in each trial arm completed the health-related quality-of-life questionnaires (PGA, SF-36, FACIT-fatigue and EQ-5D) at each assessment time point. Please clarify the reasons for incomplete capture of this information such as loss to follow-up or exclusion of patients for specific reasons (e.g. use of escape therapy).

Response

Table 5 below provides details of the number of patients with a record for each HRQoL questionnaire at each time point. This includes all observed data and no imputation has been used. Missing data is a result of early withdrawal from study or a missed assessment.

Unfortunately, the reasons for incomplete capture of individual health-related quality of life questionnaires were not captured on the case report forms (CRFs). The CRF asked the investigator to indicate whether the questionnaire was administered. If yes, a date had to be provided. If no, there was no requirement to provide a reason.

- PGA was assessed at Baseline, Week 12, Week 24, Week 36, Week 48 and Week 52. It could also be assessed at the early withdrawal visit (if relevant).
- SF-36 (PCS and MCS) was assessed at Baseline, Week 12, Week 24, Week 36, Week 48 and Week 52. It could also be assessed at the early withdrawal visit (if relevant).
- FACIT-Fatigue Score was assessed at Baseline, Week 24, Week 48 and Week 52. It could also be assessed at the early withdrawal visit (if relevant).
- EQ-5D was assessed at Baseline, Week 12, Week 24, Week 36, Week 48 and Week 52. It could also be assessed at the early withdrawal visit (if relevant), and/or at an unscheduled visit.

Table 5: Patients who completed PROs at each timepoint

Patients completed PRO / patients completed blinded treatment	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Baseline				
SF-36 PCS	48	49	97	49
SF-36 MCS	48	49	97	49
PGA VAS	49	51	100	49
FACIT-Fatigue	50	49	99	49
EQ-5D	50	49	99	49
Week 12				
SF-36 PCS	49	51	97	49
SF-36 MCS	49	51	97	49
PGA VAS	49	51	96	49
FACIT-Fatigue	-	-	-	-
EQ-5D	49	51	96	49
Week 24				
SF-36 PCS	46	46	90	46
SF-36 MCS	46	46	90	46
PGA VAS	47	47	90	46
FACIT-Fatigue	47	49	95	46
EQ-5D	47	47	91	46
Week 36				
SF-36 PCS	44	47	85	42
SF-36 MCS	44	47	85	42
PGA VAS	46	46	87	41
FACIT-Fatigue	-	-	-	-
EQ-5D	46	46	86	41
Week 48				
SF-36 PCS	43	45	82	40
SF-36 MCS	43	45	82	42
PGA VAS	44	46	84	41
FACIT-Fatigue	45	47	81	40
EQ-5D	44	45	84	40
Week 52				
SF-36 PCS	43	45	85	39
SF-36 MCS	43	45	85	39
PGA VAS	44	43	85	40
FACIT-Fatigue	44	45	84	40
EQ-5D	44	45	85	39

Note that FACIT-Fatigue assessments were only carried out at Baseline, Week 24, Week 48 and Week 52.

GiACTA Part 2

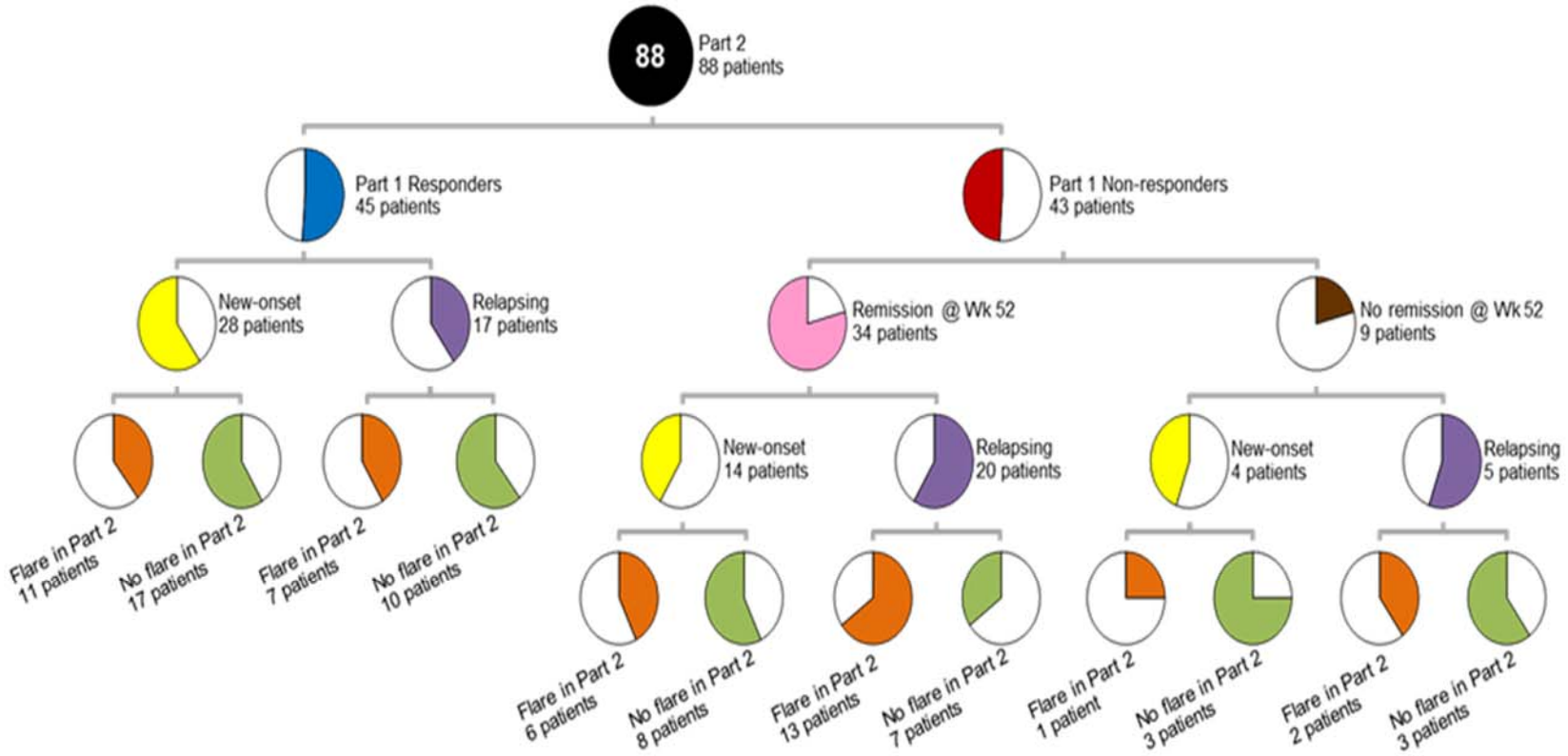
A10.

Figure 7 on page 54 of the submission presents the patient disposition in part 2 of GiACTA by response. Please split the non-responder branch by new onset/relapsed disease to match the responder branch.

Response

Figure 7 in the submission was a graphical representation of the patient disposition described verbally in the Regulatory Dossier. Whilst the Regulatory Dossier provides detail on the new-onset / relapsed disease status of responders, it does not provide such a breakdown for the non-responders. However, such information can be obtained from the database listing, which showed that, of the 43 patients from Part 1 who were non-responders, 18 patients (42%) had new-onset disease and 25 patients (58%) had relapsing disease. See Figure 2 on next page.

Figure 2: Updated disposition of Part 2 patients



Important note: the figure represents the disposition of patients in Part 2, including their baseline characteristics and their overall Part 1 outcome. It is not an analysis of the outcome of Part 2 in relation to the blinded treatments received in Part 1. As such, treatment arms from Part 1 are not shown. It must be borne in mind that the 'Part 1 responders group' (blue) and the 'Part 1 non-responders group' (red) are represented by patients from all four of the Part 1 treatment groups.

A11.

On page 56 of the submission it states that, "[redacted]*"*

Please provide the actual figures behind this statement. In addition please provide the baseline (i.e. at the start of Part 1) disease status (newly diagnosed or relapsing) for each row of Tables 19 and 20.

Response

All the data available to us for the open-label extension have been shared to date. However, we would like to note the following limitations:

- these are not part of a formal interim analysis, therefore cannot be considered as a robust evidence base, and were only included in the dossier for full transparency
- there only are extremely small numbers of patients in each segment restricts any clear or robust conclusions being possible
- the design of this open-label extension allowed physician choice of treatment, leading to substantial cross-over of patients between tocilizumab exposure (and non-exposure) in Part 1 and Part 2, as well as changes in background concomitant medications, such as GCs and methotrexate

Section B: Clarification on cost-effectiveness data

B1. Priority question:

There appears to be an error in the calculation of QALYs. This relates to 2 aspects; (i) the length of time patients experience a lower utility value as the result of a flare; and (ii) the proportion of patients who are in subsequent remission (not experiencing a flare). These issues are described in turn below:

i. *Patients who have a flare move to the flare state for 1 cycle (1 week) and receive the utility value associated with this state. However, these patients are excluded from the remission state for 4 weeks in the QALY calculation (column BC in sheet "TCZ (QW) arm" and column BB In sheet "CS (52Wk) arm"). This means that these patients appear to spend 3 weeks accruing no health-related quality-of-life.*

Response

This correction has been performed and an updated model is provided as a separate excel file. The utility on flare has been linked with the cumulative proportion of patients on the 4 weeks frame, in order to account for the equal proportion of patients who are deducted from the remission health state who had no utility attributed to them for 3 weeks.

ii. *When calculating QALYs 'on Remission', the proportion of patients in subsequent remission (second component of formulae in column BC in sheet "TCZ (QW) arm" and BB in sheet "CS (52Wk) arm") is estimated as being the proportion of patients in the "Subsequent Remission (on escape steroid regiment)" state minus the proportion in the "Cumulative flare 4 weeks (for disutility)" column. This approach can result in negative QALYs for the second component of the formulae for QALYs 'on Remission' (i.e. a negative proportion of patients in subsequent remission).*

Response

The first 4 cycles of the submitted model had a very small negative proportion of patients generated between cumulative 4 week proportion on flare and on subsequent remission. This resulted from the fact that in the first model cycles, patients on flare (moving from sustained and subsequent remission states) were higher than those from sustained remission, simply because it takes 2 to 3 cycles for the cohort to circulate from sustained remission to flare and then to subsequent remission. After that time point, this negative proportion ceases to be generated. We addressed this issue by setting the proportion to

zero if a negative value was generated, so that utility will be attributed purely to those who were on the other 2 exclusive health states (flare or sustained remission)

Please correct these errors and submit a revised Excel model. Please also provide a description of the corrections to the model, together with a complete set of corrected results.

Response

Please see separate document for updated Sections B.3.7 and B.3.8, which have been re-presented with ICERs calculated from the re-submitted model.

For clarification questions: B2-B3, please report the results based on the corrected model.

Response

We can confirm, all the below questions have been addressed using an updated model, which incorporates the amends described in B1 and the subgroup analysis requested in B3.

B2. Priority question:

Please provide tables similar to Tables 49 and 50 in the submission for the probabilistic base-case results for the intention-to-treat population.

Response

Table 6 and Table 7 show the probabilistic base-case results for the intention-to-treat population.

Table 6: Probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Prednisone alone	[redacted]	12.42	8.44	[redacted]	0.02	0.45	[redacted]
Tocilizumab with prednisone	[redacted]	12.44	8.88				

Table 7: Probabilistic base-case results with the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Prednisone alone	[redacted]	12.42	8.43	£12,083	0.02	0.45	£30,579
Tocilizumab with prednisone	[redacted]	12.44	8.89				

B3. Priority question:

As requested in the NICE scope, please provide additional analyses and results for the following subgroups: (i) New-onset giant cell arteritis and (ii) Relapsing giant cell arteritis. The relevant input data for these subgroups appears to be already included within the 'Parameters-SAS outputs NPH' sheet. Specifically, please provide for each subgroup:

a) *Base-case result tables (deterministic and probabilistic).*

b) *Figures of the scatter plots and cost-effectiveness acceptability curves.*

c) *Revised figures (Figs 10, 11) and tables (Table 34) for time to first flare transition probability*

d) *Revised table (Table 35) for the transition probability to subsequent flares*

Response

The GiACTA trial included the following GCA population subgroups, i) newly diagnosed and ii) a combination of relapsed and refractory patients. Limited data were available within the model submitted to NICE on 10th August, as further analysis of the subgroup data was needed. Additional data is now included in the re-submitted model, on the sheet 'Model parameters – subgroup data', which includes: baseline characteristics, utility data, transition probability for TTFF and TTSF, starting GC dose, and health-state unit costs.

While the subgroup analysis has been included it's important to note that the efficacy of tocilizumab is not statistically significantly different between these two populations. Also, since the GiACTA trial was not powered to detect any difference in treatment effect between these population subgroups the data analysis is limited. Moreover, the real world data used to extrapolate the GC dose for GCA patients, is not available according to these population subgroups, so we had to assume they are the same.

Furthermore, while these population subgroups were defined in the GiACTA trial, and then in the NICE scope, it's important to note that clinicians in England treating GCA have reported they do not consider patients according to these definitions, and there are no standard definitions for relapse and refractory in the GCA community.

The analysis requested in B3 a-d is presented in Appendix 1.

B4. Priority question:

Please incorporate additional functionality in the revised Excel model to allow the user to select the following populations and associated parameter inputs: (i) Intention-to-treat; (ii) New-onset and (iiii) Relapsing.

Response

The model submitted with these clarification questions now includes the option to choose between calculating the cost-effectiveness for the following subpopulations: i) ITT, ii) newly diagnosed, and iii) relapsed/refractory populations of GCA patients.

B5. Priority question:

The model potentially double counts costs during a flare episode. The model appears to attribute a 3-month flare cost at the point of a flare (i.e. during a specific cycle of 1 week duration). However, for the next 11 weeks these patients still appear to receive other management costs as well. Please confirm whether our understanding is correct and provide further justification for the assumptions.

Response

Substantial, regional variations exist across the UK in how GCA patients are managed within the NHS. For example, some regions have fast track pathways where GCA patients can have an appointment with the rheumatologists within a week, other regions manage patients via telephone consultations between the GP and rheumatologists, and in some regions GCA patients are managed by their GP. Therefore, to quantify the management costs of GCA within the NHS as accurately as possible, a third party agency was commissioning to perform market research of over 100 clinicians treating GCA across England. The market

research analysis (presented in B8) of the management of GCA showed it's a complicated paradigm, with many different specialties involved.

During the market research, clinicians were specifically asked how management of a flare differed from the usual management of a GCA patient who was well controlled (Table 43 of the submitted dossier). It also varies by region how long after a flare a GCA patient received additional management costs for. Therefore, a reasonable approach seemed to be to apply the mean flare management costs only once at the beginning of the flare event (week 1). Since the management costs of controlled GCA were reported separately from flare costs these background costs were applied around the flare.

Full details of how the Research Partnerships insights on management costs are mapped to the health states within this model are described in section B.15.

B6. Priority question:

There are several aspects of the model which require further clarification in relation to external validity. In particular:

a) *The mean number of flares (19.67) predicted over a 30-year period appears high for the glucocoticosteroids alone comparator. Proven et al (2003) reported a maximum of 7 flares in any patient based on a median follow-up of 10-years compared with the current model predictions of 10.35 relapses over the same period (i.e. over 1 relapse/year). Similarly, Larbaca et al (2015) reported a median relapse rate of 0.4 relapses/year (IQR 0.21-0.64) over a median duration of 5-years (i.e. approximately 2 relapses over 5 years compared with the current model predictions of 5.26 over the same period).*

Please provide further clarification on the validation undertaken and any additional evidence to support the external validity of the predicted number of flares.

Response

The mean number of flares over the lifetime of a GCA patients is challenging to estimate given the range of clinical uncertainty and heterogeneity among the GCA population.

An advisory board of rheumatologists and ophthalmologists working in GCA clinics across England were asked to estimate the number of flares per year for a GCA patient. The group consensus was that the number of flares depended on whether the patient experienced a

flare/relapse or were able to taper their GC dose without experiencing a flare/relapse. The collective view of the ad board attendees was:

- [redacted] of GCA patients would be able to taper their GC dose over approximately [redacted]
- [redacted] of GCA patients would have a relapsing/refractory GCA which required continuous titration up and down of GCs over a period of approximately [redacted]
- [redacted] of GCA patients would require a long-term GC maintenance dose for [redacted], where their GCA was controlled at a stable dose, but attempting to withdraw GC all together would cause a flare/relapse at any time after diagnosis

This highlights that not only is the number of flares/relapses uncertain for GCA patients, but that the duration which a patient is at risk of a flare/relapse is also [redacted]. This is compounded by the absence of any predictive characteristics for which patients will require which treatment approach.

Together this makes the estimation of the average number of flares over a lifetime very difficult for a GCA patient, both in the short and the long term.

Since the GiACTA trial is the most robust RCT in GCA patients available the approach taken in the submitted model was to assume the difference measured in the trial was continued beyond the trial. The limitation of linking the GiACTA trial to the stated published literature is that these articles are observational studies, with no standardised GC tapering regimen, and no randomisation of patients.

b) *It is also unclear whether patients who are reported in 'flare at visit' during consecutive follow-up times (e.g. at weeks 44 and 48) are being treated as multiple or single counts in estimating the time to subsequent flare transition probability. If consecutive periods of flare are being treated as multiple counts, please present an additional sensitivity analysis based on re-estimating the weekly probability of flare assuming that flares reported over consecutive follow up periods are treated as a single flare episode.*

Response

If a patient is in a flare state for consecutive assessments, for example at Weeks 44 and 48, these would be counted as distinct flare events, for a total of 2 flares.

However, this only affects 5 patients in the PBO+52 arm and no patients among the tocilizumab QW arm, so the analysis is not expected to substantially impact the cost-effectiveness calculations.

c) *The selected parametric distribution (exponential) for the prednisone strategy predicts that less than 2% of patients receiving glucocorticosteroids will not have experienced a first flare by 5 years. Several longitudinal cohort studies with follow-up data beyond 5 years (e.g. Proven 2003, Alba 2014, Larbaca 2015, Restuccia 2016) report a significantly higher proportion of patients receiving glucocorticosteroids that have not experienced a flare by 5 years (approximate range 30-50% across studies). Furthermore, these studies also appear to suggest that the hazard of relapse/recurrence tends to decrease during long-term follow-up, suggesting reduced disease activity over time (Cid and Alba, 2015). Please provide further justification to support the selected parametric distribution and any additional evidence to support the external validity of the longer term predictions.*

Response

The parametric distribution was chosen as it was considered to be the best statistical fit for the GiACTA data considering both Akaike Information Criterion (AIC) and visual inspection. Additionally, applying a piecewise distribution, instead of the parametric, does not substantially alter the extrapolation and the number of patients not experiencing a flare.

With regards to the external validity of this extrapolation, as described in the response to B6a above, there is substantial variability between clinical opinions sought by Roche and published articles regarding the rate of flare/relapse and the time a GCA patient is at risk of these. This variability meant that we were unable to unanimously validate or dismiss some assumptions, nor we were able to find a suitable alternative.

Additionally, the number of flares/relapses modelled from the GiACTA data at one year is equal to number of flares/relapses reported in some published literature after longer periods of time.

B7. Priority question:

A key feature of the base-case analysis is the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration. This is justified in Table 31 on the basis that "early results from the OLE (open label extension study) suggest that very few patients re-flare after treatment with tocilizumab". However, Table 48 (and data reported in section B2.6.6) later state that "50% of patients relapsed/flared after withdrawing tocilizumab therapy". This figure appears similar to that reported by Adler et al (2016) following cessation of tocilizumab in the previous RCT, where the authors concluded that "clinical and serologic remission in response to TCZ (tocilizumab) for 52 weeks does not result in relapse-free survival after termination of treatment".

a) *Please provide further justification to support the appropriateness and validity of this key assumption.*

b) *Please present further justification for why data reported in either or both the open label extension study and/or Adler et al (2016) studies were not formally used.*

Response

As an amendment, Table 31 of the submitted dossier should read "**early results from the OLE (open label extension study) suggest *not all* patients re-flare after treatment with tocilizumab**".

We have not formally considered the OLE data to inform the duration of treatment benefit for the reasons summarised in the response to A11.

Roche recognise the duration of treatment benefit attributed to tocilizumab in the treatment of GCA patients is highly uncertain and highly impactful on the cost-effectiveness estimate. We have attempted to engage clinical opinion on this area of uncertainty, both during the dossier development and again in response to these clarification questions. However, clinical opinion varied, and clinicians were also highly uncertainty on this point.

The uncertainty around estimates of the duration of tocilizumab treatment benefit are related to the uncertainty - and heterogeneity - regarding the duration of treatment required for GCA currently and the natural aetiology of GCA, as summarised in the response to B6.

Roche agrees that a proportion of GCA patients will experience flare/relapse, a proportion of patients will see long term benefit from a short treatment period, and other GCA patients require lifelong therapy to prevent constant flaring/relapsing. However, there is substantial uncertainty, and variability, regarding these proportions.

B8.

Please provide the full report for the market research reference (Research Partnerships 2017).

Response

The market research was performed by a third party organisation to inform business insights and gather information regarding how GCA is managed in the NHS. Therefore, the only report developed where the questions were merged into themes of relevance for modelling, including confidence intervals and with text explanation of the implications was the report submitted to NICE with the dossier. Therefore, any extensive additional write up of the full business insights would require more time to prepare than we have here for the clarification questions' responses.

Following the scheduled teleconference with NICE and the ERG on the 6th September 2017 it was recommended to prioritise preparing the background and context of the data reported in Tables 43, 44 and 45 of the submitted dossier - the management costs of GCA in the NHS.

The individual clinician responses to the questions that were combined into Tables 43, 44 and 45 of the submitted dossier are included in the attached excel file.

In addition, the original data tables from the market research report are re-presented below, here including the number of responders for each question (n/N) (Table 8, Table 9, Table 10). The data incorporated into the cost-effectiveness model is shown with underlined and bolded text.

If more information is required we will be able to report it given longer timelines.

Table 8: Physician type to whom patients will typically initially present if signs or symptoms of GCA recur1 (England) - Table 43 of the submitted NICE dossier, derived from Table 17 of the market research report

% physicians	Physicians to whom patients will initially present if signs or symptoms recur						
	GP	Ophthalmologists	A&E	Rheumatologists	Neuro	Geriatricians	Other
England (*N*=102):	**59% (60/102)**	**7% (7/102)**	**5% (5/102)**	**25% (25/102)**	**1% (1/102)**	**2% (2/102)**	**2% (2/102)**
95% CI	***(49.5%-68.5%)***	***(2.0%-12.0%)***	***(0.8%-9.2%)***	***(16.6%-33.4%)***	***(0%-2.9%)***	***(0-%4.7%)***	***(0%-4.7%)***
Rheumatologists (*N*=37):	54% (20/37)	3% (1/37)	3% (1/37)	35% (13/37)	0% (0/37)	0% (0/37)	5% (2/37)
95% CI	*(37.9%-70.1%)*	*(0%-8.5%)*	*(0%-8.5%)*	*(19.6%-50.4%)*	-	-	*(0%-12.0%)*
General Practitioners (*N*=29):	72% (21/29)	3% (1/29)	7% (2/29)	17% (5/29)	0% (0/29)	0% (0/29)	0% (0/29)
95% CI	*(55.7%-88.3%)*	*(0%-9.2%)*	*(0%-16.3%)*	*(3.3%-30.7%)*	-	-	-
Ophthalmologists (*N*=17):	35% (6/17)	29% (5/17)	12% (2/17)	24% (4/17)	0% (0/17)	0% (0/17)	0% (0/17)
95% CI	*(12.3%-57.7%)*	*(7.4%-50.6%)*	*(0%-27.4%)*	*(3.7%-44.3%)*	-	-	-
Geriatricians (*N*=14):	71% (10/14)	0% (0/14)	0% (0/14)	14% (2/14)	0% (0/14)	14% (2/14)	0% (0/14)
95% CI	*(47.2%-94.8%)*	-	-	*(0%-32.2%)*	-	*(0%-32.2%)*	-

A&E physicians (*N*=5):	60% (3/5)	0% (0/5)	0% (0/5)	20% (1/5)	20% (1/5)	0% (0/5)	0% (0/5)
95% CI	*(17.1%-100%)*	-	-	*(0%-55.1%)*	*(0%-55.1%)*	-	-

[1]Responses to the question (T14): "Please think specifically of patients whose signs or symptoms recur or have raised ESR (attributable to GCA) during the initial treatment / glucocorticoid dose tapering period. When symptoms initially recur, to which physician type / where would the patient typically present?"

Table 9: Proportion of GCA patients managed after diagnosis by each key clinical manager (England, N=108) - Table 44 of the submitted NICE dossier, derived from Table 6 of the market research report

	Primary decision maker[1] (PQ28a)	Involved in long-term follow-up[2] (PQ28b)	Involved managing dose tapering[3] (PQ28c)
Rheumatologist	**66% (71/108)**	66% (71/108)	67% (72/108)
95% CI	***57%-75%***	*57.1%-74.9%*	*58.1%-75.9%*
General Practitioner	**17% (18/108)**	61% (66/108)	38% (41/108)
95% CI	***10%-24%***	*51.8%-70.2%*	*28.8%-47.2%*
Geriatrician	**10% (11/108)**	15% (16/108)	13% (14/108)
95% CI	***4.3%-15.7%***	*8.3%-21.7%*	*6.7%-19.3%*
Ophthalmologist	**5% (5/108)**	15% (16/108)	11% (12/108)
95% CI	***1%-9%***	*8.3%-21.7%*	*5.1%-16.9%*
Neurologist	**2% (2/108)**	3% (3/108)	2% (2/108)
95% CI	***0%-4.5%***	*0%-6.1%*	*0%-4.5%*
Other	**1% (1/108)**	1% (1/108)	2% (2/108)
95% CI	***0%-2.8%***	*0%-2.8%*	*0%-4.5%*

[1]Responses to the question (PQ28a): "Please think about the current management of this patient. Who is the primary decision maker regarding the ongoing management of this patient's GCA?"

[2]Responses to the question (PQ28b): "Are any other physicians involved in the patient's long-term follow-up?"

[3]Responses to the question (PQ28c): "And, are any other physicians involved in managing this patient's glucocorticoid dose tapering schedule?"

Table 10: Frequency of follow-up by patient sub-group1 (England) - Table 45 of the submitted NICE dossier, derived from Table 7 of the market research report

% physicians	Weekly	Every 2 weeks	Monthly	Every 2 months	Every 3 months	Every 6 months	Less frequently
Treatment naïve GCA patients (*N*=36)[2] (T10a)	17% (6/36)	14% (5/36)	19% (7/36)	14% (5/36)	8% (3/36)	11% (4/36)	17% (6/36)
95% CI	*(4.7%-29.3%)*	*(2.7%-25.3%)*	*(6.2%-31.8%)*	*(2.7%-25.3%)*	*(0%-16.9%)*	*(0.8%-21.2%)*	*(4.7%-29.3%)*
GCA newly diagnosed patients (*N*=112)[3] (T10b)	**10% (11/112)**	**24% (27/112)**	**29% (32/112)**	**12% (13/112)**	**12% (13/112)**	**6% (7/112)**	**8% (9/112)**
95% CI	***(4.4%-15.6%)***	***(16.1% - 31.9%)***	***(20.6% - 37.4%)***	***(6.0%-18.0%)***	***(6.0%-18.0%)***	***(1.6%-10.4%)***	***(3.0%-13.0%)***
GCA patients on maintenance therapy (*N*=110)[4] (T10c)	**0% (0/110)**	**2% (2/110)**	**20% (22/110)**	**13% (14/110)**	**30% (33/110)**	**24% (26/110)**	**12% (13/110)**
95% CI	**-**	***(0%-4.6%)***	***(12.5% - 27.5%)***	***(6.7%-19.3%)***	***(21.4% - 38.6%)***	***(16.0% - 32.0%)***	***(5.9%-18.1%)***
GCA relapse and refractory patients (*N*=102)[5] (T10d)	**4% (4/102)**	**18% (18/102)**	**29% (30/102)**	**14% (14/102)**	**22% (22/102)**	**9% (9/102)**	**5% (5/102)**
95% CI	***(0.2%-7.8%)***	***(10.5% - 25.5%)***	***(20.2% - 37.8%)***	***(7.3%-20.7%)***	***(14.0% - 30.0%)***	***(3.4%-14.6%)***	***(0.8%-9.2%)***
Glucocorticoid free remission patients (*N*=95)[6] (T10e)	**0% (0/95)**	**0% (0/95)**	**1% (1/95)**	**8% (8/95)**	**17% (16/95)**	**26% (25/95)**	**47% (45/95)**
95% CI	-	-	*(0%-3.0%)*	*(2.5%-13.5%)*	*(9.4%-24.6%)*	*(17.2% - 34.8%)*	*(37.0% - 57.0%)*

[1]Responses to the question (T10a-e): "How frequently do you personally have follow-up appointments with patients in each of the following groups?"

[2](T10a) "Patients diagnosed with GCA who are not initiated on therapy"

[3](T10b) "Newly-diagnosed patients (prior to the start of glucocorticoid dose-tapering) or who are undergoing glucocorticoid dose-tapering (or other treatment) and not experiencing recurrence of symptoms"

[4](T10c) "Patients who have undergone glucocorticoid dose tapering (or other treatment) and currently receive low dose glucocorticoids"

[5](T10d) "Patients whose symptoms recurred during the initial treatment / glucocorticoid dose tapering period"

[6](T10e) "Patients who have successfully undergone glucocorticoid dose tapering (or other treatment) and are currently in glucocorticoid-free remission"

The data within Table 45 of the submitted dossier was also incorporated into the cost-effectiveness model, evaluated as follows:

- The “proportion of frequency of follow up (on remission + off steroid)” was modelled using market research data for the “Glucocorticoid free remission patients (N=95)” group;
- The “proportion of frequency of follow up (on remission + on steroid)” was modelled using market research data from the following three groups, “GCA newly diagnosed patients (n=112)”, “GCA patients on maintenance therapy (n=110)”, and “GCA relapse and refractory patients (n=102)”;
- The “proportion of frequency of follow up (on remission + on maintenance)” was modelled using market research data from the following two groups “GCA patients on maintenance therapy (n=110)”, and “GCA relapse and refractory patients (n=102)”.

B9. Priority question:

The risk of giant cell arteritis related complications (loss of vision and stroke) assumes a surrogate relationship between these and relapse/flare events and that these risks are modifiable with treatment with tocilizumab. Please provide further justification and/or references to support these assumptions.

Response

The only HTA evaluation published to date in GCA - which considers different diagnostic approaches - reported the rates of vision loss decrease after diagnosis, which we take as a proxy for the onset of treatment and patient monitoring. (Luqmani et al. 2016) Additionally, the risk of stroke reported here for GCA patients was low throughout.

It is assumed there are no differences in diagnosis or referral of GCA for treatment between now and when tocilizumab is available clinically. Therefore, the only difference in this model is when a patient has uncontrolled GCA during flare/relapse, then the risk of vision loss or stroke is increased due to ischaemic complications.

The importance of the risk of vision loss and stroke for GCA patients was discussed at a clinician advisory board but was immediately dismissed as being of low concern to the attendees, unless a patient was experiencing flare/relapse - but even then it was easily managed.

The only association between tocilizumab treatment and the risks of vision loss and stroke in the model, is indirectly via the decreased rates of flare/relapse - which is taken directly from the GiACTA trial.

B10. Priority question:

Our understanding is that patients in England and Wales would be likely to be treated with prednisolone rather than prednisone. The current price of prednisolone (5 mg, 28 tablets = £0.81) is lower than that assumed for prednisone (5 mg, 30 tablets = £26.70). Please provide further justification for assuming the cost of oral prednisone rather than prednisolone and present an additional scenario assuming the lower acquisition cost of prednisolone.

Response

Prednisone was costed in the cost-effectiveness model since this was the treatment included in the GiACTA trial.

However, we agree that prednisolone is both recommended in the GCA Guidelines. (Dasgupta et al. 2010) Therefore, the re-submitted model has been updated to replace prednisone costs with prednisolone costs as the comparator treatment in the base case, rather than a scenario analysis. This change in comparator treatment costs adds [redacted] to the submitted base case.

All results presented herein are using the data from the GiACTA trial for prednisone but the costs for prednisolone.

B11. Priority question:

The GiACTA clinical study report (page 47) states that the first 4 subcutaneous injections of tocilizumab required administration in a setting where medications and resuscitation facilities were available and patients were required to stay for 2 hours following each injection. It also states that patients and caregivers were trained to perform the subcutaneous injections at their first visit and that clinical staff could administer the injections if a patient was unable or unwilling to self-administer. Please provide:

a) *Clarification on whether patients would require administration of their initial injections in a health care facility in routine clinical practice and any associated resource use and cost implications for the NHS.*

Response

Roche currently offer rheumatoid arthritis (RA) patients and hospital Trusts a funded, homecare delivery service for tocilizumab, which we are looking to continue for GCA patients. This service includes up to two home visits by a qualified nurse, to train the GCA patient to self-administer subcutaneous tocilizumab. While we do not know the rate that Trusts would take up this service for GCA patients, for RA patients there is a 90% uptake of homecare delivery, with the remaining 10% of patients being a combination of those collecting from the hospital pharmacy and those requiring hospital-based administration.

The homecare training costs [redacted] per nurse visit with up to two nurse visits included, but is fully funded by Roche.

For those Trusts choosing not to take up the Roche-funded homecare training, it is assumed that the administration training would be incorporated into a standard nurse appointment for prescribing tocilizumab, so would have no additional costs to the NHS.

b) *An estimate of the resource and costs required to train and support a patient and/or carer to self-administer tocilizumab.*

Response

See B11a.

While we do not yet know the rate of uptake for homecare-based training for GCA patients, there is no reason to assume it would be different to RA. Additionally, clinicians and nurses were of the opinion that GCA patients or their carers would be capable to self-administer subcutaneous tocilizumab.

In addition to the 2 nurse-based training visits, Roche also fund a nurse-based Health Check service via the telephone. RA patients are called weekly for the first month, then fortnightly for the next month (up to 6 calls in total). The purpose of the Health Check service is to enquire into a patient's overall well-being, and give advice and counselling where needed on self-administration techniques for tocilizumab.

c) *The proportion of patients in GiACTA who were unable to or unwilling to self-administer tocilizumab and discuss any associated resource and cost implications for the NHS.*

Response

It was not recorded during the GiACTA trial how many patients were unable or unwilling to self-administer tocilizumab, the reason for not self-administering was also not recorded.

As stated in B11a and b, the majority of GCA patients are expected to be able to self-administer tocilizumab.

During the Scottish Medicines Consortium submission for subcutaneous tocilizumab to treat RA, it was assumed up-to 10% of patients could require a district nurse to assist with injections. However, this number was criticised during the appraisal as being too high. (Scottish Medicines Consortium 2014)

While we recognise that GCA patients and RA patients differ, we hope that providing the homecare uptake rates in RA patients allows insight regarding subcutaneous tocilizumab self-administration in a real clinical practice.

B12.

Please provide further details on the data from the MarketScan database used to inform the cumulative glucocorticosteroid dose equation parameters.

Response

Section B3.3.4 of the submitted dossier presented the equations used to inform the cumulative GC dose for GCA patients not receiving tocilizumab. These equations were based on analysis of prescriptions of GC for GCA patients within the US MarketScan database, the full data behind these equations is presented below in sections B.12.1 to B.12.4.

Patient demographics

Study cohort descriptions are listed in Table 11. GCA was diagnosed in [redacted] patients in the US MarketScan database from 2000 to 2015. The MarketScan GCA cohort had [redacted] to GCA patients (Table 11); the patients were predominantly female and elderly. The mean age was [redacted] years. There were no data available in the MarketScan dataset for body mass index, smoking history, or alcohol use.

Table 11: Baseline demographics for GCA patients from the MarketScan database

	US MarketScan n (%)
n	[redacted]
Study time frame	[redacted]
Average follow-up time years (median)	[redacted]
Demographic Characteristics at Baseline	
Female	[redacted]
Mean age at index [SD]	[redacted]
Age Group	
50-54	[redacted]
55-59	[redacted]
60-64	[redacted]
65-69	[redacted]
70-74	[redacted]
75-79	[redacted]
80-84	[redacted]
>84	[redacted]

Patient comorbidity levels at baseline

In the [redacted] (Table 12).

Table 12: Comorbidities at baseline (12 month prior to GCA index date)

	US MarketScan [redacted] **# of events (%)**
Charlson Comorbidity Index	
Rheumatic disease	[redacted]
Cerebrovascular disease	
COPD	
Diabetes mellitus	
Peripheral vascular disease	
Any Malignancy, including Lymphoma and Leukemia, except Malignant Neoplasm of Skin	
Congestive heart failure	
Renal disease	
Liver disease	
Myocardial infarction	
Peptic Ulcer disease	
Dementia	
Hemiplegia or paraplegia	
Metastatic solid tumor	
AIDS	
Glucocorticoid-related adverse conditions and events	
Blood pressure (hypertensive events)	
Glucose tolerance	
Eye conditions	
Bone related conditions	
Neuropsychiatric disorders	
Skin conditions	
Muscle & tendon disorders	
Gastrointestinal tract disorders	
Endocrine disorders	
Other comorbidities	
Serious infection	
Anaemia	
Cataracts	
Polymyalgia rheumatic	
Glaucoma	
Osteoporosis	
Fracture	
Diabetes with chronic complications	
Depression	
Diabetic neuropathy	
Diabetic retinopathy	
GI perforation	
Adrenal insufficiency	
Aseptic necrosis of bone	

GC use

The mean daily starting dose of oral GC among all GCA patients in the MarketScan cohort [redacted] was [redacted] and the median was [redacted] (Table 5). The mean cumulative dose of oral GC at 26 weeks and 52 weeks from the first GC dose was [redacted] and [redacted], respectively. [redacted] GCA

patients assessed had [redacted] of GC by 26 weeks and over [redacted] of GC by 52 weeks.

Of the patients that were evaluated for their full follow-up time [redacted] in the study, the average number of days that patients were on GC was [redacted] and [redacted]. The mean cumulative GC dose for the full study period was [redacted] and the median was [redacted].

Taper Statistics

The MarketScan GCA cohort took on average (mean) [redacted] to taper the GC dose down to 10 mg/day, [redacted] to taper down to 7.5 mg/day, [redacted] to taper down to 5 mg/day and [redacted] to taper to down to 0 mg/day (sustained for 60 days).

Claims data are limited in that if a physician alters the dose instructions from the original GC prescription based on GCA symptoms, the billed claim would not capture the change. Additionally, prescription treatment gaps in healthcare claims may not imply a discontinuation of GC treatment or a true taper to 0. Therefore, we estimated the taper statistics to 0 mg/day only among patients who have complete prescription data suggesting that they reached at least 10 mg/day in GC dose.

This was done to avoid inaccuracy in the taper length and missing prescription data. In addition, sustained taper to 0, was defined based on no evidence of a new GC prescription for 30 days and 60 days. We present results for both sustained definitions in Table 13; however, the 60-day sustained taper to 0 mg/day is more conservative and more clinically meaningful.

Among the patients reaching a GC dose of 10 mg/day or less [redacted], only [redacted] patients were able to taper their dose to 0 and remain GC-free for 60 days within 52 weeks. Additionally, of those patients, approximately [redacted] restarted glucocorticoids within a mean time of [redacted].

When follow-up time is extended beyond 52 weeks, approximately [redacted] of patients taper to 0 mg/day and sustain the taper for at least 60 days. The average time to taper to 0 mg/day is [redacted]

Table 13: Summary of GC use in US real-world data (MarketScan)

Average daily steroid starting dose of first GC after index (mg)	
n	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Daily steroid dose 26 weeks from index (mg)	
n¥	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Cumulative steroid dose 26 weeks from index (mg)	
N	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Patients on 0 mg/day at 26 weeks*, n (%)	
Daily steroid dose 52 weeks from index (mg)	
n¥	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Cumulative steroid dose 52 weeks from index (mg)	
N	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Patients on 0 mg/day at 52 weeks*, n (%)	
Cumulative steroid dose from index to end of study (mg)	
n	[redacted]
Mean (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Total mean (median) days' supply of GC	
Days to reach GC taper of 10 mg/day	
n (patients)	[redacted]
Mean	
Q1	
Q2 (median)	
Q3	

Min	[redacted]
Max	
Days to reach GC taper of 7.5 mg/day	
n (patients)	[redacted]
Mean	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Days to reach GC taper of 5 mg/day	
n (patients)	[redacted]
Mean	
Q1	
Q2 (median)	
Q3	
Min	
Max	
n (% of patients) tapered to 0 mg/day maintained for 30 days*	
At 26 weeks	[redacted]
At 52 weeks	
Days to reach GC taper of 0 mg/day maintained for 30 days (within 52 weeks from index)Δ	
n (%) patients who taper to 0 mg/day within 52 weeks	[redacted]
Mean (days)ß among patients who reach 0 mg/day within 52 weeks	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Patients who restarted GC, n(%)	
Among patients who restarted GC: mean duration (days) sustained at 0 mg/day	
Days to reach GC taper of 0 mg/day maintained for 60 days (within 52 weeks from index) Δ	
n (%) patients who taper to 0 mg/day within 52 weeks	[redacted]
Mean (days)ß among patients who reach 0 mg/day within 52 weeks	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Patients who restarted GC, n (%)	
Among patients who restarted GC: mean duration (days) sustained at 0mg/day	
Days to reach GC taper of 0 mg/day maintained for 30 days (using all follow-up data)Δ	
n (%) patients who taper to 0 mg/day	[redacted]
Mean days among patients who reach 0 mg/day (SD)	
Q1	
Q2 (median)	
Q3	
Min	
Max	
Patients who restarted GC, n(%)	
Among patients who restarted GC: mean duration (days) sustained at 0 mg/day	
Days to reach GC taper of 0 mg/day: maintained for 60 days (using all follow-up data)Δ	
n (%) patients who taper to 0 mg/day	[redacted]
Mean days among patients who reach 0 mg/day (SD)	
Q1	

Q2 (median)	[redacted]	
Q3	[redacted]	
Min	[redacted]	

¥Only patients who had a fill during week 26 or 56 were included, which means that patients could be excluded if they tapered to 0 mg/day or were still on glucocorticoids but their prescription fill that was not during week 26 or week 52.

ΔPatients must have had at least one fill for a glucocorticoid less than or equal to 10 mg/day to be included in the taper analysis. There were 3,852 out of 4,804 patients who met these criteria, which is 80.2% of the full cohort.

ßObserved days to reduce to 0 mg/day are less than observed days to reduce to 5 mg/day due to differences in the underlying cohorts. Patients who reduced to 0 mg/day are a subset of the full cohort (as described above) and are likely less severe compared to the rest of the cohort because they reached 10 mg/day during their glucocorticoid treatment.

GC exposure

Oral GC exposure was captured using the mean prednisone-equivalent dose observed over time. Since there is no uniform unit of measurement among GC, conversion of dosages to prednisone equivalents (PEQ) is necessary. The PEQ of various agents are specified below. For pharmacy-based prescriptions, the total dosage per prescription was calculated first by multiplying the metric quantity in each prescription by its strength, then the prednisone equivalent for the prescription was calculated (by GC class) using the following conversion factors:

[redacted]

The index date for the GC exposure is the first date of GC use after the date of first GCA diagnosis index date

In addition, to the above approach, to describe the real world GC-tapering schedule that physicians follow with GCA patients, cumulative GC use over time is provided at 6 months, 12 months, and at the end of the study period using all available follow up duration.

The equations used to inform the cumulative GC dose for GCA patients not receiving tocilizumab were based on US MarketScan data and not the CPRD analysis, because the CPRD only allowed prednisolone use to be captured as cumulative dose. Since the majority of the CPRD cohort lacked complete daily dose instructions with their prescription fills, so the data presented on daily dose are limited to those patients with complete data [redacted], while the full cohort [redacted] is used to describe the cumulative dose of oral GC. To calculate the cumulative oral prednisolone dose we combined information from tablet strength (i.e., 10 mg or 5 mg) and prescription quantity, summed across all prednisolone prescriptions (in mg). Hence, the data granularity needed for informing equivalent equations from CPRD were not available at the time of submission, but research is on-going.

The GCA prescription data describing both US MarketScan and UK CPRD GCA patients are still being analysed and being prepared for publication.

B13. Priority question:

The EQ-5D analyses reported in Tables 15 and Figure 5 of the submission exclude post-escape EQ-5D data (GiACTA clinical study report, page 533). Please provide results including post-escape data based on the repeated measures model used for other endpoints, including the same covariates and interactions: treatment, starting prednisone dose (<=30mg/day, >30mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction.

Response

The EQ-5D data presented in Table 15 and Figure 5 of the submitted dossier only includes the VAS score, this data was not incorporated into the cost-effectiveness modelling. The cost-effective model incorporated all EQ-5D-based utility values for flare, including those measured post-escape therapy. The covariates are discussed in turn below.

In the submitted dossier, all EQ-5D-based utility values were aggregated to measure the impact of flare on quality of life - including pre- and post-escape regimen and across treatment arms. These data were aggregated since so few flares were recorded in the GiACTA trial, therefore this approach allowed the biggest data set to measure the impact of a flare on quality of life. This is in agreement with clinical opinion. Table 14 shows the number of flares reported in the GiACTA trial: in total, by treatment arm, and according to

GC dose. In total, 147 of the 250 patients didn't experience a flare, and [redacted]. A total of 168 flares were experienced by a total of 103 patients in the GiACTA trial. Table 14 also shows the number of flares according to GC dose when the flare occurred: a total of [redacted] and [redacted]. This indicates there is [redacted] again this is in agreement with clinical opinion.

Table 14: Number of flares/relapses in the GiACTA trial

Number of flares	Total number of patients in GiACTA	Number of patients in the PBO 26 week arm	Number of patients in the PBO 52 week arm	Number of patients in the TCZ QW arm	Number of patients in the TCZ Q2W arm	GC dose <= 30 mg	GC dose >30 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]. This demonstrates that no difference is expected for the following co-variates, which are all related to time: visit, treatment-by-visit interaction, starting dose-by-visit interaction, and baseline score-by-visit interaction.

Regarding the request to analyse utility according to the co-variate of starting dose, this analysis has reported [redacted]. The utility value according to the co-variate of starting dose is reported in Table 15 comparing against the value used in the submitted model.

Table 15: Flare utility values, comparing the submitted model and the starting dose co-variate analysis

	Submitted model	**Analysed with co-variate of starting dose**
No flare utility estimate	0.7713	[redacted]
Flare utility estimate	0.6420	[redacted]

The cost-effectiveness model takes the assumption that all patients return to baseline quality of life after a flare/relapse event, so there is no overall reduction in quality of life with repeated flares.

B14. Priority question:

Please provide additional clarification on the specification and output of the mixed model used to inform health state utilities.

Response

The mixed model used to inform the health state utilities is described in Section B.3.4.5 of the submitted dossier. The model includes the states of flare and non-flare as covariates, as well as the baseline EQ-5D-based utility score. The data presented above show there is no significant relationship between time and utility, and Table 15 shows that using starting dose as a covariate will have minimal impact on the ICER.

i. *how the analysis addresses the mismatch between the 4-week duration of flare and the frequency of the planned EQ-5D assessments*

Response

The GiACTA trial data captures the utility value of a flare/relapse event occurring in close vicinity of a scheduled assessment visit. The GiACTA trial data is unable to capture the evolution of utility values further away from this assessment. As a result, published literature and market research were used to inform how long a flare/relapse would impact a patient's quality of life. (Dasgupta et al. 2010)

ii. *why subsequent flares were excluded and any implications this has for the analysis.*

Response

As described in the response to question B13 above, all flares were included in the analysis for the cost-effectiveness model, since so few flares/relapse were reported across the GiACTA study (Table 14).

However, this may be misinterpreted since the qualitative analysis presented in Figure 19 of the submitted dossier only included first flares. The reason was to aid the demonstration that the clinical opinion of a 4-week flare duration was corroborated by the GiACTA data, and since an anchor point was needed for time in this graphical representation then only first flares were included in this plot.

B15.

Please provide further clarification on Tables 43 and 44 in the submission. It is unclear how the data in these tables relate to the specific health states.

Response

To avoid the risk of overestimating management costs and ensure the data incorporated best matched the health states modelled here, not all of the data reported in Tables 43 and 44 of the submitted dossier were included in the cost-effectiveness model - section B8 outlines what data were included.

For the costs associated with a flare/relapse, the data in Table 43 of the dossier were used. These were applied as a one-off costs, and not to calculate per cycle cost for health states. To inform Table 43 of the dossier, two data tables from the market research were combined, to calculate the cost of managing a flare:

- Information on the proportion of visits which should be allocated to each type of specialist for the first flare visit is based upon Table 17 of the market research: physician type to whom patients will typically initially present if signs or symptoms of GCA recur

- Information on the proportion of visits which should be allocated to each type of specialist for the subsequent flare visits is based upon Table 18 of the market research: proportion of GCA patients management during flare

The mean number of visits for a flare (2.71) is also taken from page 29 of the market research.(Research Partnerships 2017)

The data in Table 44 of the dossier were used to calculate the management costs for the ‘on remission + on steroid’, ‘on remission and off steroid’ and ‘on remission and maintenance steroids’ health states. Since more detailed information wasn’t available, to specifically match the health states to the market research, then we assumed these costs were the same for patients in all states. Again, for simplicity and to avoid the risk of double counting costs, only information on the primary decision maker was used for costing purposes. This information is taken from Table 6 of the market research data (proportion of GCA patients managed after diagnosis according to clinical speciality).

While considering the market research data behind Table 45 in the submitted dossier, it was found that the average proportions were not calculated from the original numbers (n/N) but

were averaged from the previously reported percentages. This was an oversight on our behalf, and the table presented above in B8 Table 10 now includes the corrected percentages for these reported proportions, the difference is compared below in Table 16. These amended proportions have been incorporated into the re-submitted dossier, but only change the ICER by ~£150/QALY.

Table 16: Frequency of visits for GCA management

Management frequency	Proportion of frequency of follow up (on remission + on steroid)		Proportion of frequency of follow up (on remission + off steroid)		Proportion of frequency of follow up (on remission + on maintenance)	
	Submitted proportion	**Corrected proportion**	Submitted proportion	**Corrected proportion**	Submitted proportion	**Corrected proportion**
Weekly	4.72%	**4.6%**	0.00%	**0.0%**	1.92%	**1.9%**
Every 2 weeks	14.64%	**14.5%**	0.00%	**0.0%**	9.70%	**9.4%**
Monthly	25.94%	**25.9%**	1.00%	**1.1%**	24.33%	**24.5%**
Every 2 months	12.97%	**12.7%**	8.00%	**8.4%**	13.48%	**13.2%**
Every 3 months	21.26%	**21.0%**	17.00%	**16.8%**	26.15%	**25.9%**
Every 6 months	13.06%	**13.0%**	26.00%	**26.3%**	16.78%	**16.5%**

B16.

In Table 47 (summary of model variables in base case), please clarify what the variables "treatment in primary care only" and "primary care referral to specialist care" represent and how these relate to the health states and/or assumptions of the model.

Response

The lines "treatment in primary care only" and "primary care referral to specialist care" in Table 47 of the submitted dossier were included in error in the submission. These were relevant to an early model stage, prior to the market research project being completed so should have been removed from Table 47. These data were replaced in the model with the tables and descriptions presented above.

Section C: Textual clarifications and additional points

C1.

The PRISMA flow diagram on page 43 and the description of the search results on page 42 of the Appendix refers to, "Literature database searches yielded 1,014 records. Additionally, two records were identified and included through other sources." However, there is no description of what these other sources were, and how the 2 records were identified. Please provide these details.

Response

The structured searches in Embase, Medline and Cochrane retrieved 1014 citations. Additionally, supplementary searches (bibliography and conference searching) identified two more publications.

Kyle et al (1989) (Kyle and Hazleman 1989), which is one of the 21 extracted primary studies included in our systematic literature review, was identified from the bibliography of the Buttgereit et al (2016) systematic review. (Buttgereit et al. 2016) This was not retrieved from structured searches as it didn't include the indexed term or title/abstract term for 'random' or 'RCT' for the study design facet.

The second reference (Stone 2016) was an abstract for the GiACTA trial and was included via hand searching of conference proceedings for the last 3 years. (Stone et al. 2016) This has been extracted as a secondary link for the GiACTA trial

Appendix 1: In response to B3a-d, *Section B.3.9 Subgroup analysis* of the dossier is included below based on the re-submitted model

A. **Base-case result tables - deterministic and probabilistic.**
B. **Figures of the scatter plots and cost-effectiveness acceptability curves.**
C. **Revised figures (Figs 10, 11) and tables (Table 34) for time to first flare transition probability**
D. **Revised table (Table 35) for the transition probability to subsequent flares**

The following population subgroups were defined *a priori* in the GiACTA trial (Tuckwell 2015; Stone et al. 2017):

- Newly diagnosed: GCA patients who have not yet received treatment
- Relapsed/refractory: GCA patients who have received GC treatment and either not responded (refractory) or responded but their GCA has relapsed/flared again (relapsed).

The subgroup analysis for these populations is provided below, with the methods used to update each of the inputs to the economic model described in turn.

1.1 Baseline characteristics

A summary of the baseline characteristics of the GiACTA trial for the ITT population and the population subgroups is shown in Table 17.

In the GiACTA study, 47 patients had newly-diagnosed GCA and 53 patients had relapsed/refractory GCA in the tocilizumab arm, while 23 patients had newly-diagnosed GCA and 28 patients had relapsed/refractory GCA in the placebo arm.

Table 17: Baseline demographics and disease characteristics for GiACTA trial (All-patient population)

	ITT		New Onset		Relapse & Refractory	
	TCZ-QW n=100	PBO + 52-week GC taper n=51	TCZ-QW n=47	PBO + 52-week GC taper n=23	TCZ-QW n=53	PBO + 52-week GC taper n=28
Age, years, mean (SD)	69.5 (8.5)	67.8 (7.7)	69.6 (8.7)	68.6 (7.9)	69.5 (8.4)	67.1 (7.6)
Females, n (%)	78 (78)	37 (73)	37 (79)	17 (74)	41 (77)	20 (71)
Race/Ethnicity, n (%)						
Black or African American	2 (2)	1 (2)	1 (2.1)	0	1 (1.9)	1 (3.6)
Other	96 (96)	49 (96)	45 (95.7)	23 (100)	51 (96.2)	26 (92.9)
White	2 (2)	1 (2)	1 (2.1)	0	1 (1.9)	1 (3.6)
Unknown	0	0	0	0	0	0
Weight, kg, mean (SD)	69.8 (13.8)	73.1 (15.3)	67.7 (13.5)	66.9 (12.7)	71.7 (13.9)	78.3 (15.6)
BMI (SD)	26.0 (4.4)	25.8 (4.1)	25.0 (4.05)	24.0 (3.31)	26.8 (4.59)	27.3 (4.21)
Prednisone dose, n (%)						
≤30 mg/day	52 (52.0)	26 (51.0)	15 (31.9)	10 (43.5)	37 (69.8)	16 (57.1)
>30 mg/day	48 (48.0)	25 (49.0)	32 (68.1)	13 (56.5)	16 (30.2)	12 (42.9)
Disease duration, days, mean (SD)	306.8 (563.5)	255.2 (435.5)	29.2 (10.2)	26.5 (10.5)	553.0 (687.7)	443.1 (519.5)
Signs or symptoms of GCA,[a] n (%)	37 (37.0)	24 (47.1)				
Symptoms of PMR,[b] n (%)	59 (59.0)	35 (68.6)				
Erythrocyte sedimentation rate, mm/h, mean (SD)	24.6 (18.7)	24.2 (18.2)	23.8 (22.1)	19.2 (15.2)	25.3 (15.2)	28.4 (19.6)
Diagnosis by positive temporal artery biopsy, n (%)	57 (57.0)	29 (56.9)				
Diagnosis by positive imaging, n (%)	50 (50.0)	23 (45.1)				

(Hoffman-La Roche Ltd. 2016; Stone et al. 2017)
[a]Signs and symptoms of GCA: new-onset localised headache, scalp tenderness, or temporal artery tenderness, decreased pulsation, or jaw or mouth claudication.
[b]Symptoms of PMR: morning stiffness and/or pain in the shoulder and/or hip girdles.
BMI: body mass index; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; SD: standard deviation

1.2 Utility data for subgroups

Patients enrolled in the GiACTA trial completed the EQ-5D-3L questionnaire at baseline and at weeks 12, 24, 36 and 48. The same as for the ITT population analysis, remission and relapse/flare health state utilities were estimated from the GiACTA trial data using a mixed effects model separately for each subgroup, adjusting for baseline utility.

Table 18 and Table 19 show the estimated utilities from GiACTA data for each subgroup. These estimates are consistent with the estimates for the ITT population showing poorer quality of life (lower utility weights) when patients relapse/flare. A flare event was determined by the investigator and was defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA. Quality of life whilst on remission was lower in the relapsed/refractory population compared to new onset patients, but they were comparable during a flare.

Table 18: Utilities from GiACTA trial used in the cost-effectiveness modelling – New Onset

Health State	Estimate	Std. Error	P-Value	Lower 95 CI	Upper 95 CI	Justification
On remission	0.8115	0.00907	<0.0001	0.7937	0.8294	GiACTA data
On Flare	0.6451	0.03573	<0.0001	0.5749	0.7153	GiACTA data

Table 19: Utilities from GiACTA trial used in the cost-effectiveness modelling – Relapse and Refractory

Health State	Estimate	Std. Error	P-Value	Lower 95 CI	Upper 95 CI	Justification
On remission	0.7333	0.00964	<0.0001	0.7144	0.7523	GiACTA data
On Flare	0.6343	0.03333	<0.0001	0.5688	0.6998	GiACTA data

1.3 Clinical parameters and variables

Clinical parameters for the model were derived from the pivotal GiACTA trial data for each of population subgroup using the same methods as for the ITT population for: time to first flare; time to subsequent flare and cumulative steroid dose.

1.3.1 Summary of transition probabilities

The transitions used in the model and the data sources are summarised in Table 33 of the submitted dossier and only the changes related to the addition of subgroups are discussed in more detail in the following sections.

1.3.1.1 Time to first flare transition probability

Standard parametric models were fitted to the Kaplan-Meier curves for time to first flare (TTFF), in the same way as was done for the ITT population. The goodness of fit assessment was based on both the statistical index of Akaike Information Criterion (AIC) and visual inspection.

Following standard NICE guidelines in economic evaluation (Latimer 2013), the log-cumulative hazard plots were generated for the two treatment arms modelled from GiACTA, presented for the newly diagnosed (Figure 3) and the relapsed/refractory population subgroups (Figure 4).

Figure 3: Log of negative-log of estimated survivor function for the newly diagnosed subgroup

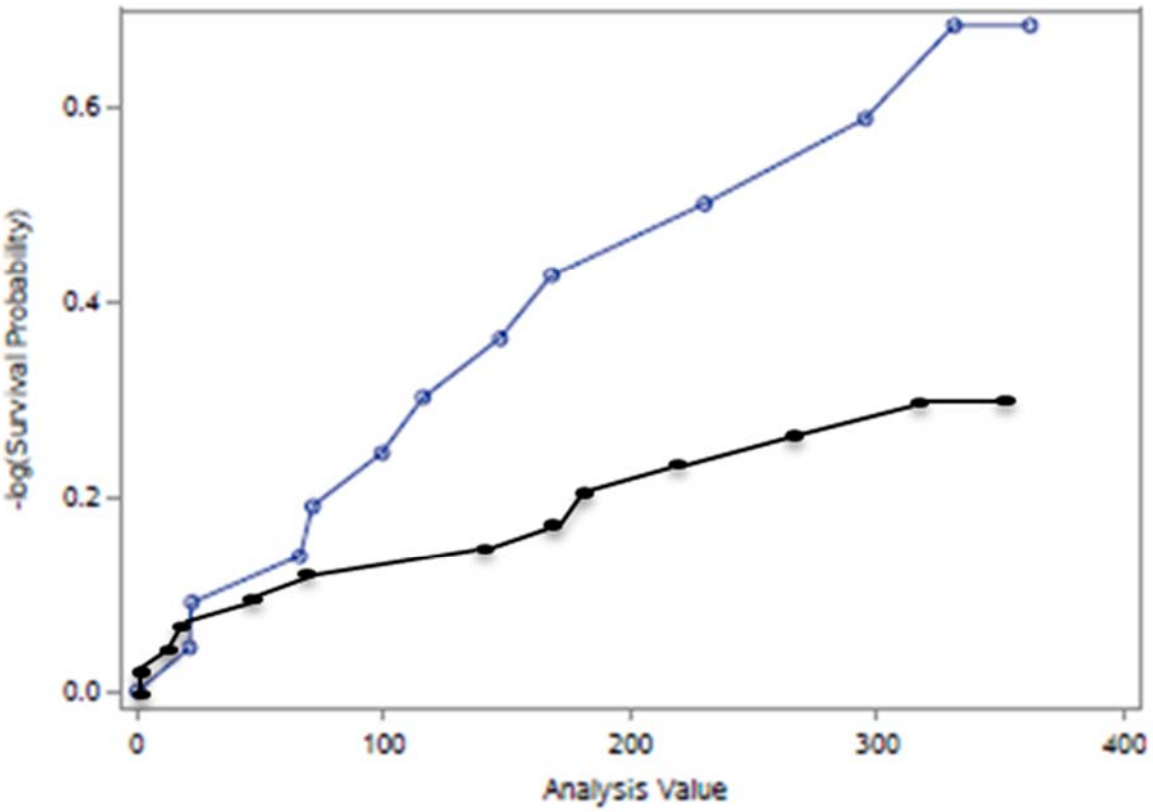


Figure 4: Log of negative-log of the survivor function for the relapsed/refractory subgroup

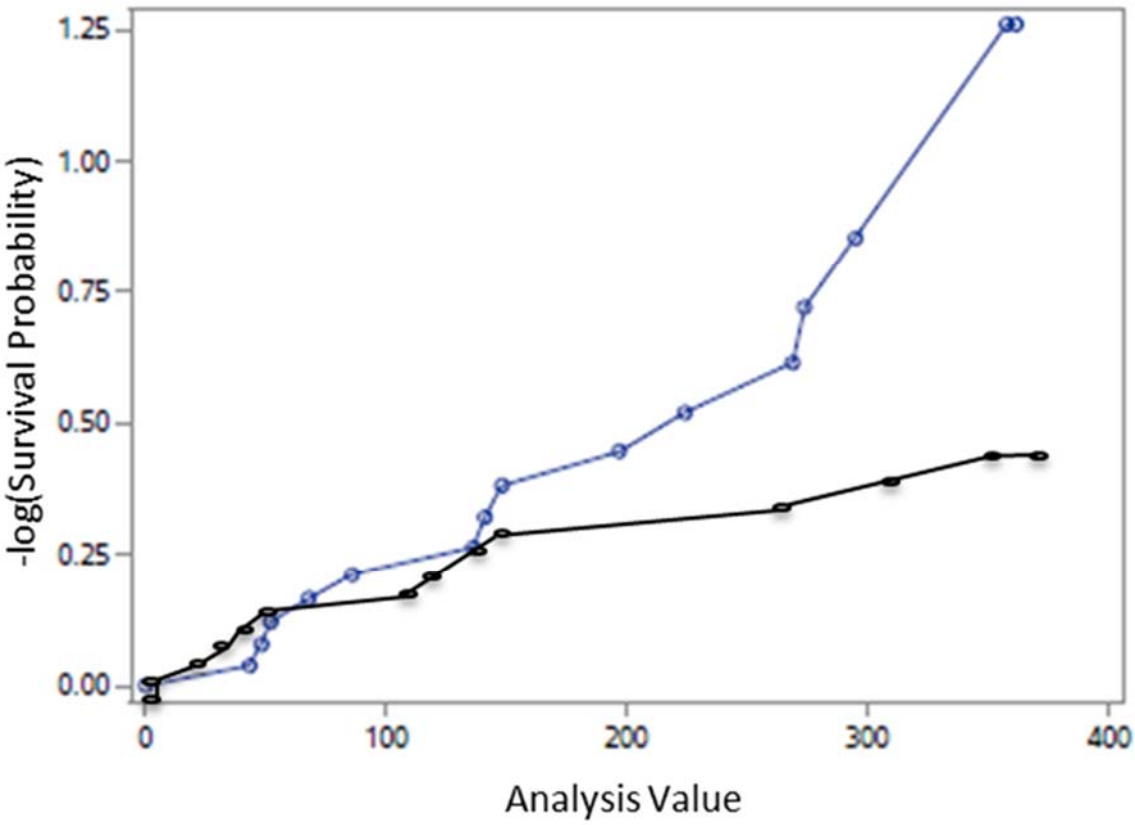


Table 20 shows the AIC estimates for each treatment arm and each separate parametric model assessed for the ITT population and each subgroup. The shadowed cells indicate the model that was selected as the base case, which is the Weibull for TCZ QW arm and the Exponential for the placebo arm for ITT population. For each subgroup, the same parametric distribution as the ITT population was assumed in the base case for consistency.

Table 20: AIC for parametric fit on TTFF

	ITT population		New Onset		Relapse & Refractory	
	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper
EXPONENTIAL	176.33073	118.04365	85.42530	59.11030	92.89860	60.57836
WEIBULL	174.88006	119.03899	85.68266	61.10613	93.19271	60.20129
LNORMAL	175.02922	118.10141	85.73792	60.33805	93.28869	59.88400
GAMMA	176.82294	118.10068	87.66579	62.20861	95.15233	62.08643
LLOGISTIC	174.90303	118.81808	85.71293	60.79097	93.18509	60.46400

Figure 5 illustrates the KM curves for each treatment arm and the base case parametric models used for extrapolation: Weibull for TCZ QW + 26-week GC taper and exponential for PBO QW + 52-week GC taper groups. Figure 6 and Figure 7 illustrate the same for the 'New Onset' and 'Relapse & Refractory' subgroups respectively.

Figure 5: Parametric extrapolation of time to first flare (GiACTA data – ITT population)

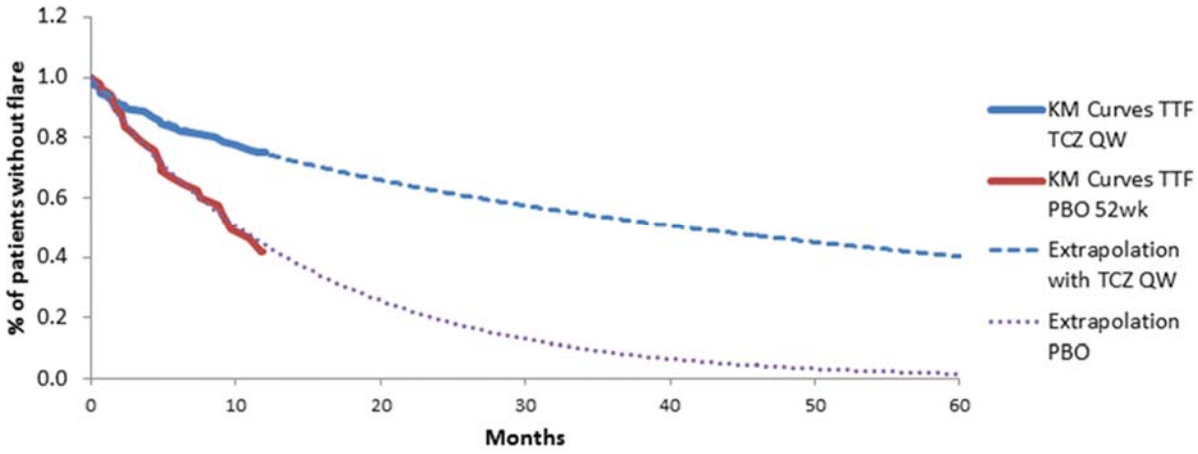


Figure 6: Parametric extrapolation of time to first flare (GiACTA data – New Onset population)

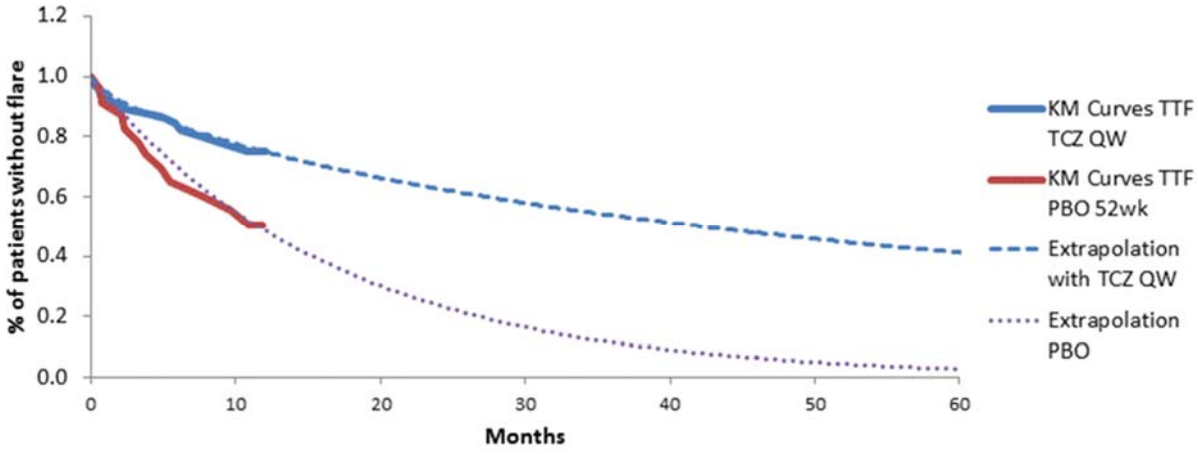
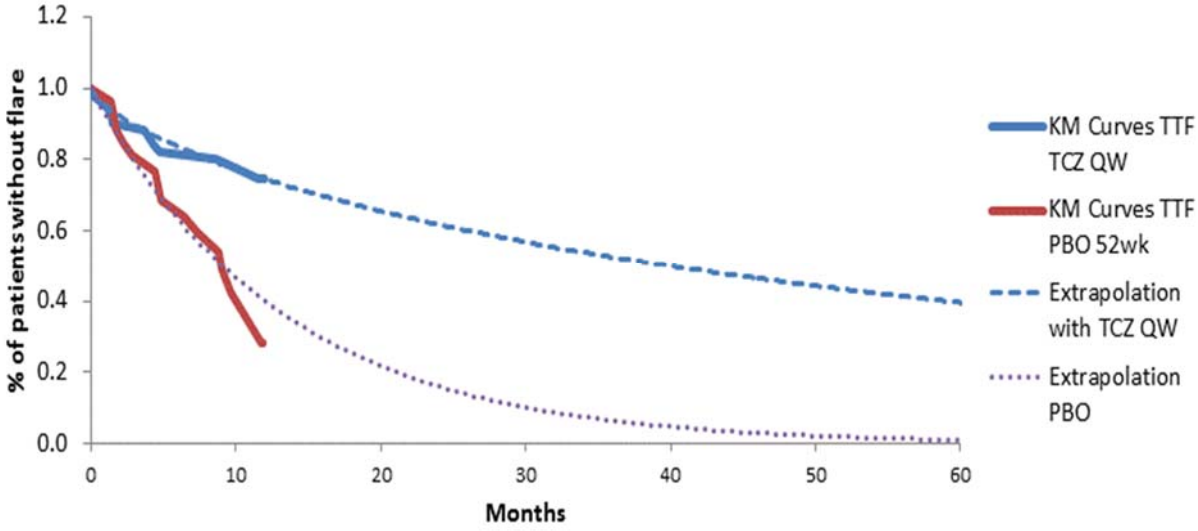


Figure 7: Parametric extrapolation of time to first flare (GiACTA data – Relapse & Refractory population)



1.3.1.2 Time to subsequent flare transition probability

The rate of subsequent flares was estimated from the GiACTA data using a Poisson regression, in the same way as for the ITT population. The time frame of the analysis was defined from the time of the first flare for each individual patient until the end of the follow up, in order to observe the number of subsequent flares within the defined timeframe. The rate of subsequent flares for each treatment arm was normalised by using the average time after first flare and until the end of the follow-up, as observed for each treatment arm in the GiACTA trial. Finally, the rates were converted to weekly transition probabilities to fit the model cycle length. Weekly probability of subsequent flare is substantially higher in the placebo arm than in the tocilizumab arm. Table 21 shows estimated cycle-specific transition probabilities to subsequent flares from GiACTA trial data for ITT population and each of the subgroups.

Table 21: Transition probability to subsequent flares calculated from GiACTA trial data

Population	Treatment arm	Mean rate (in log scale)	Standard Error	Mean days follow-up used within the analysis	Weekly probability of flare
ITT	Tocilizumab QW	-1.056	0.354	228	0.0106
	Placebo 52 week	-0.300	0.224	224	0.0228
New Onset	Tocilizumab QW	-0.875	0.447	228	0.0127
	Placebo 52 week	-0.619	0.378	224	0.0166
Relapse & Refractory	Tocilizumab QW	-1.299	0.577	228	0.0083
	Placebo 52 week	-0.074	0.277	224	0.0285

1.3.1.3 Prednisone dose for each treatment arm is based on GiACTA trial data

- **During primary remission (until first flare)**: defined by the trial protocol and therefore kept the same as the ITT population.

- **During secondary remission (after first flare)**: kept the same as the ITT population in the absence of robust real-world estimates for the subgroups in the comparator arm.

- **During relapse/flare**: A predictive equation of the GC dose increase due to the relapse/flare was estimated per treatment arm, based on GiACTA trial data. The last effective dose is the prediction coefficient of the size of the GC dose increase due to flare. This increased GC dose is maintained for a week. This was an assumption that was considered to be conservative based on clinical input and given the potentially acute nature of the event.

[redacted]

Table 22: Predicted GC dose increase for flare event

	ITT		New Onset		Relapse & Refractory	
	Estimate	Standard error	Estimate	Standard error	Estimate	Standard error
Tocilizumab arm coefficient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS arm coefficient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.4 Health-state unit costs and resource use

Unit costs per visit are sourced from NHS reference costs for each follow up visit and converted to 'per cycle' costs using the frequency of visits (Table 23) sourced from the market research study. The model estimates per cycle costs for the ITT population or the subgroup (depending on user selection) before applying to the proportion of patients receiving each specialist visit to calculate the average resource use cost for each health state. The proportion of frequency of follow up (on remission + on steroid) is different for subgroups

Table 23: Frequency of visits for GCA management

Management frequency	Proportion of frequency of follow up (on remission + on steroid)			Proportion of frequency of follow up (on remission + off steroid)	Proportion of frequency of follow up (on remission + on maintenance)
	ITT	New Onset	Relapse & Refractory	ITT/subgroups	ITT/subgroups
Weekly	4.6%	10.0%	4.0%	0.0%	1.9%
Every 2 weeks	14.5%	24.0%	18.0%	0.0%	9.4%
Monthly	25.9%	29.0%	29.0%	1.1%	24.5%
Every 2 months	12.7%	12.0%	14.0%	8.4%	13.2%
Every 3 months	21.0%	12.0%	22.0%	16.8%	25.9%
Every 6 months	13.0%	6.0%	9.0%	26.3%	16.5%

(Research Partnerships 2017)

1.5 Results for the subgroup

1.5.1 Newly diagnosed subgroup

The absolute and incremental, discounted cost-effectiveness (without PAS) results are presented in Table 24, comparing tocilizumab treatment with prednisone versus prednisone alone. Table 25 presents the discounted cost-effectiveness (with PAS) results for tocilizumab with prednisone versus prednisone alone.

Table 24: Deterministic base-case results – Newly diagnosed subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.45	9.02	[redacted]	0.00	0.35	[redacted]
Tocilizumab with prednisone	[redacted]	12.45	9.38				

Table 25: Deterministic base-case results – Newly diagnosed subgroup (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.45	9.02	£13,202	0.00	0.35	£37,334
Tocilizumab with prednisone	[redacted]	12.45	9.38				

A probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations to determine the the uncertainty surrounding the base case ICERs for the newly diagnosed population subgroup, as conducted for the ITT population. The absolute and incremental, discounted cost-effectiveness results are presented without then with the PAS, in Table 26 and Table 27. The scatter plots and the corresponding cost-effectiveness acceptability curves (with and without PAS applied) are shown in Figure 8,

Figure 9, Figure 10, Figure 11.

Table 26: Probabilistic base-case results – Newly diagnosed subgroup (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.42	8.44	[redacted]	0.002	0.45	[redacted]
Tocilizumab with prednisone	[redacted]	12.44	8.88				

Table 27: Probabilistic base-case results – Newly diagnosed subgroup (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.42	8.43	£12,083	0.02	0.45	£30,579
Tocilizumab with prednisone	[redacted]	12.44	8.89				

Figure 8: Incremental cost and QALY base case results

Figure 9: Incremental cost and QALY base case results (with PAS)

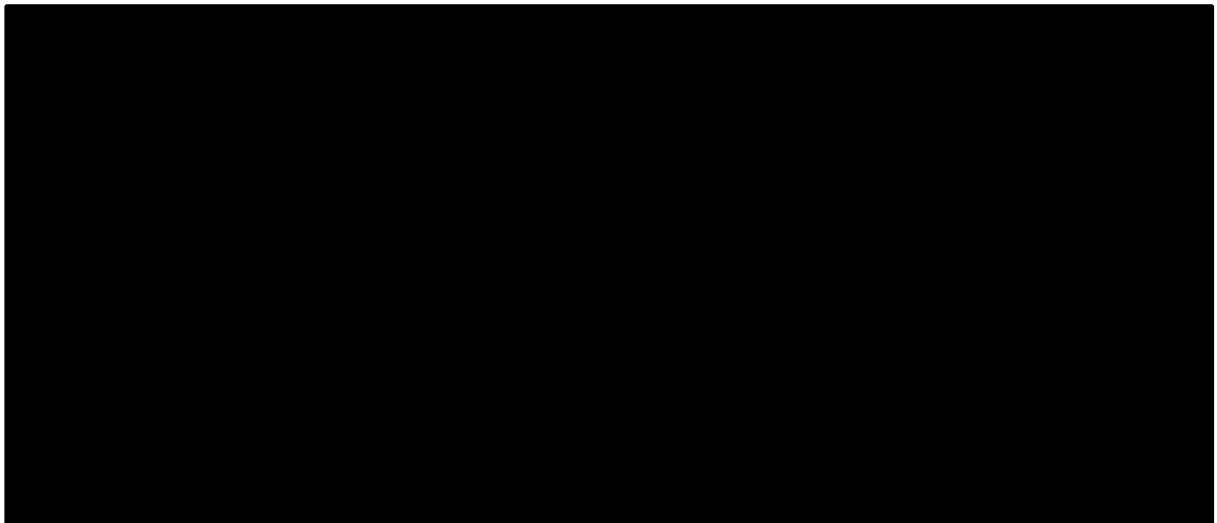
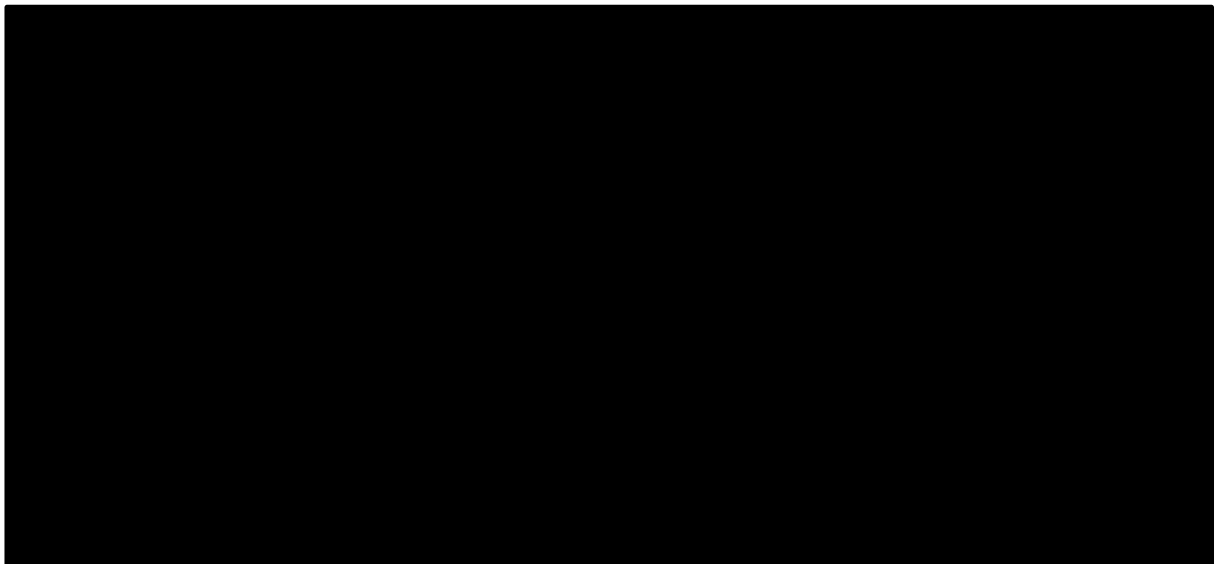


Figure 10: Cost-effectiveness acceptability curve

Figure 11: Cost-effectiveness acceptability curve (with PAS)



3.5.2 Relapsed/refractory subgroup

The absolute and incremental, discounted cost-effectiveness (without PAS) results are presented in Table 28, comparing tocilizumab treatment with prednisone versus prednisone alone. Table 29 presents the discounted cost-effectiveness (with PAS) results for tocilizumab with prednisone versus prednisone alone.

Table 28: Deterministic base-case results – Relapsed/refractory subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.84	8.24	[redacted]	0.01	0.49	[redacted]
Tocilizumab with prednisone	[redacted]	12.85	8.73				

Table 29: Deterministic base-case results – Relapsed/refractory subgroup (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.84	8.24	£10,993	0.01	0.49	£22,403
Tocilizumab with prednisone	[redacted]	12.85	8.73				

A probabilistic sensitivity analysis (PSA) was conducted with 1,000 iterations to determine the uncertainty surrounding the base case ICERs for the newly diagnosed population subgroup, as conducted for the ITT population. The absolute and incremental, discounted cost-effectiveness results are presented without then with the PAS, in Table 30 and Table 31. The scatter plots and the corresponding cost-effectiveness acceptability curves (with and without PAS applied) are shown in Figure 12, Figure 13, Figure 14, Figure 15.

Table 30: Probabilistic base-case results – Relapsed/refractory subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.42	8.43	[redacted]	0.02	0.45	[redacted]
Tocilizumab with prednisone	[redacted]	12.44	8.89				

Table 31: Probabilistic base-case results – Relapsed/refractory subgroup (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Prednisone alone	[redacted]	12.42	8.43	£12,083	0.02	0.45	£30,579
Tocilizumab with prednisone	[redacted]	12.44	8.89				

Figure 12: Incremental cost and QALY base case results

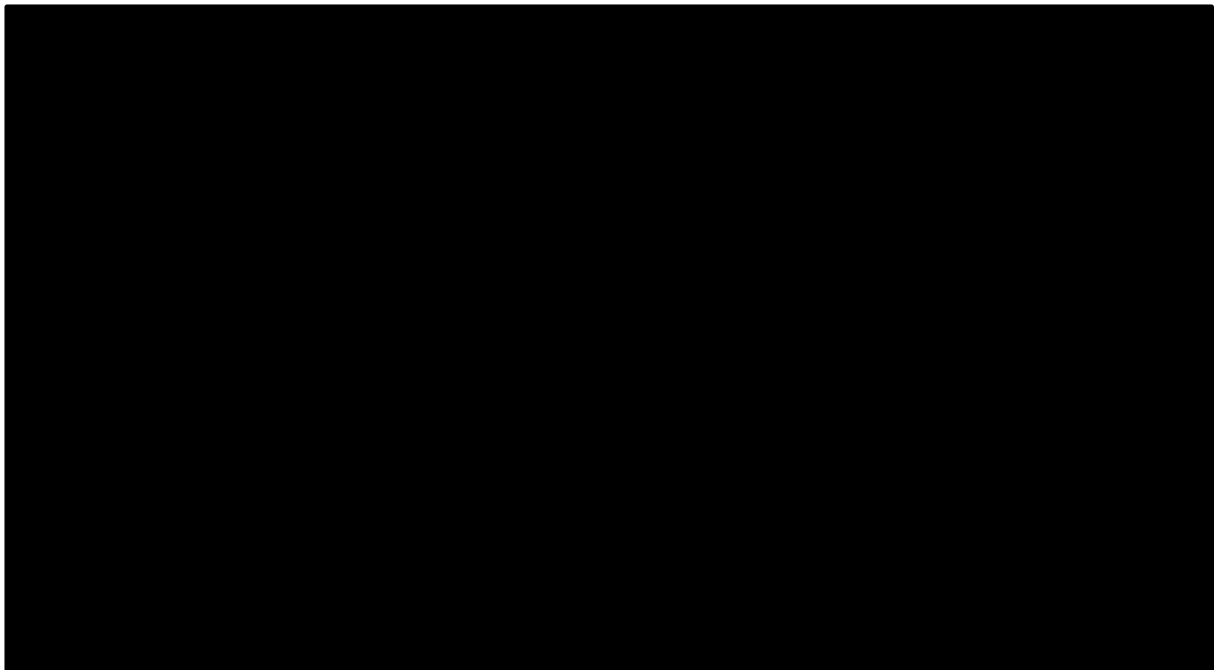
[redacted]

Figure 13: Incremental cost and QALY base case results (with PAS)

[redacted]

Figure 14: Cost-effectiveness acceptability curve

Figure 15: Cost-effectiveness acceptability curve (with PAS)



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NICE National Institute for Health and Care Excellence

Patient organisation submission

Tocilizumab for treating giant cell arteritis (ID 1051)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**John Mills**

2. Name of organisation	Vasculitis UK
3. Job title or position	Chairman
4a. Brief description of the organisation (including who funds it). How many members does it have?	VasculitisUK is the national patient support charity for those suffering from all forms of vasculitis of which there are 18 types, Giant Cell Arteritis being one of them. The charity is run entirely by unpaid volunteers and makes no charge for its services, thus the concept of "membership" is notional; however there are around 1200 people with vasculitis (or carers) on the mailing list and over 3000 subscribers to each of the online discussion groups, although there will be some duplication. The charity is funded entirely by voluntary donations from "members" & supporters and through fundraising activities.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Via our online discussion groups.**
Living with the condition	
6. What is it like to live with the condition? What do carers	Giant cell arteritis affects predominantly older people >50/60 years, incidence increasing dramatically with age. Onset of symptoms may be abrupt or insidious. It can cause sudden unexpected permanent loss of

experience when caring for someone with the condition?	sight in one or occasionally both eyes. It typically causes severe localised or generalised headaches, jaw pain, fever, fatigue, muscle pain and joint pain, anorexia & weight loss and consequent depression. The condition can be quite debilitating and the carer is often a similarly elderly spouse who may have their own health problems. The musculo-sketetal problems cause loss of mobility and in some cases results in social isolation.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatment is predominantly using high dose steroids over long periods – typically up to 2 years. This may cause serious side effects such as diabetes, osteoporosis and cataracts in a population which is already more vulnerable & compromised by age. Lesser side effects such as weight gain and loss of muscle mass can further reduce mobility. There is an increased risk of cardiovascular and cerebrovascular events either directly due to the disease or the steroids, thus an increasing need for anti-coagulants such as aspirin or warfarin. All these negative factors result in reduced quality of life for many in their latter years.
8. Is there an unmet need for patients with this condition?	Although the use of steroids is usually is quite effective in reducing symptoms, the side effects of long term steroid use can be severe. There is also a significant risk of relapse.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Anticipated benefits are greatly reduced use of steroids with consequent reduction in side effects. A further benefit would be reduced risk of relapse and long term freedom from the need for active treatment..

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There is currently no perception of disadvantages among patients & carers.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The incidence of GCA increases with age with greatest incidence in 80s +, when prospective lifespan is limited. However a significant number of sufferers are affected earlier at age 50/60. This group is at a greater risk of having to live for many years with the long term adverse consequences of steroid use such as diabetes & osteoporosis.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Although GCA is the most common type of vasculitis, it has received relatively little attention & research due to the fact that it affects predominantly the elderly and very elderly, is only very rarely a direct cause of death and can usually be readily controlled by steroids. Thus it is regarded as less important. Increasing longevity makes this attitude among medical professional less tenable and acceptable, as increasing numbers of people are likely to be living with GCA as a long-term disease and with the consequences of the heavy dependency on steroids.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	Many medical professional consider that Giant cell Arteritis is a part of the spectrum of the Large Vessel vasculitis continuum, with Takayasu arteritis affecting the lower age group, other types of vasculitis such as aortitis affecting the middle age range and GCA affecting the upper range. The use of Tocilizumab has proved highly effective in controlling Takayasu arteritis so there is good reason to expect similar benefits for the elderly, leading to a better Quality of Life in later years.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Current treatment with high dose long term steroids is detrimental to overall health.
- GCA affects predominantly the elderly and very elderly and has thus been given low priority.
- The effects of GCA & side effects of current treatment have an adverse effect on Quality of Life for many elderly people
- Increasing longevity means more people living for longer with GCA and side effects of steroids.
- Dealing with steroid side effects (diabetes, osteoporosis, cataracts) has significant repercussions in terms of Health Economics.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

Tocilizumab for treating giant cell arteritis [ID1051]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Kate Gilbert**

2. Name of organisation	Polymyalgia Rheumatica and Giant Cell Arteritis UK (PMRGCAuk)
3. Job title or position	Member (former Chair of Trustees)
4a. Brief description of the organisation (including who funds it). How many members does it have?	PMRGCAuk is a patient-led support charity founded in 2010. It now has just over 900 members. Its purpose is to provide information and support via a network of support groups, a national helpline, a website and web-based self-help forum, and a regular newsletter. The charity is funded largely by member subscription and donations. In 2016 it received a grant of £23,000 from the Wellcome Foundation for an 18-month project in the 'Engaging Science' programme. The project is called 'Research Roadshows' and presents current research at locations around the UK, bringing researchers and patients/public together.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Personal email approaches to members whom we believe to have been involved in the GiACTA study, personal messages to members of the web forum who have previously written or replied to posts regarding tocilizumab. Also in 2017 the charity carried out a survey of its members, which included items on patient concerns and priorities.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	GCA is a serious systemic vasculitis and patients feel extremely unwell at times. The first two weeks of a drop in steroid dosage can be very difficult, with returning symptoms such as headaches, jaw pain and tender scalp problems, which may trigger fears of a 'flare'. Many patients are continually fearful and anxious that any headache (perhaps caused by a minor infection) could signal a flare and a risk of sudden and irreversible blindness. This outcome is relatively rare, but an understandable anxiety that adds significantly to the burden of the illness on patients and carers. A high proportion (40-60%) of people with GCA also exhibit features of polymyalgia rheumatica, especially when their steroid dose drops below c15mg per day. This means that they are in pain all over their body, but particularly in their shoulders and hips, and their mobility is seriously affected. Living long-term with GCA puts a strain on relationships, particularly when the patient is a carer, as is often the case particularly for older females.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients tend to see GCs as a necessary evil. They hate taking them, but understand that the risk of blindness from GCA left untreated is unacceptable. At the start of treatment they are hugely relieved to be free of pain and the fear of blindness, but after a few months find that they have more difficulty reducing their dose than anticipated. They report that doctors seem more concerned about reducing their dose of steroids than they are about their symptoms. Many doctors also seem to place a greater emphasis on the results of ESR and CRP tests than on patient-reported symptoms and outcomes. Most patients with GCA do at least get to see a rheumatologist. However they are often somewhat mystified to discover that little seems to be known about their condition in comparison with, say, Rheumatoid Arthritis. In two consecutive member surveys (2012 and 2017), 'being on steroids' and 'coming off steroids' have been the highest rated concerns of patients, and reported as their main need for support.

8. Is there an unmet need for patients with this condition?	Yes. The burden of long-term health damage caused by taking steroids for several years needs to be reduced. This burden can be exacerbated for older people who may have several co-morbidities.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	TCZ offers the possibility to reduce the cumulative dosage of glucocorticosteroids over the course of the disease. It carries the advantage of targeting specific inflammatory agent in the bloodstream, as opposed to the global systemic action of GCs. Very importantly, it offers a greater likelihood of being able to reduce and eventually come off steroids without the risk of repeated relapses or 'flares'. Quote from HP a patient on TCZ: I was diagnosed with PMR GCA & LVV in 2001 & for nine years suffered constant high doses of steroids. In 2010 I was prescribed TCZ. This changed my life. Monthly infusions & I was able to reduce the steroids gradually with no ill effects. I continue to have a maintenance dose 2 monthly. I have not experienced any side effects from this drug & am able to walk & play golf as before . This is a story from one of our members CH, which appeared in the national press in July this year: By February 2016, I'd done a year on the placebo. When I was given my tocilizumab, it was like getting treasure and I couldn't wait to start. The dose was 160mg to be injected into the fleshy part of my abdomen once a week. I was monitored for the first few weeks to check for adverse reactions. Then I was taught to do it myself. Within five weeks, I looked 10 years younger and I had such amazing energy again. My stiffness and aches vanished. Sometimes, you don't realise how horrible you felt until you're feeling better. I went back to swimming, I did a yoga class three times a week and I signed up to do ballroom dancing. [redacted] joked that I was wearing him out. I took tocilizumab for a year until January this year, without any symptoms or side effects, as part of the study. I'm no longer on it but if my symptoms return, I'll be entitled to it for another 12 months. My steroids are down to 1mg a day, which I'm reassured won't do me any harm. I've no regrets about taking part in a drugs trial. I didn't feel like a guinea pig. I was treated like a private patient. If I hadn't taken part, my life would have carried on at a rather painful rate. I've since met other sufferers who have lost sight in one eye or their faces are blown-up by steroids. That could easily have been me

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some people find the method of administration of the drug cumbersome and inconvenient. Some people may have concerns about short-term toxicity of the drug. One member of our online forum (based in US) has reported: I am in the USA in the California area . [redacted]. I was put on infusions of Actemra in 2014. I had five . In that period of time I was able to reduce my prednisone from 15 to ten. After the fifth infusion I had a reaction and refused to take anymore. I leveled off at twelve prednisone. Just recently after it was approved for GCA . I tried the weekly shots. Hoping the lower dosage would be a plus. I had five samples and two regular shots. For a total of seven in all. I then felt a reaction to it aand had severe stomach disturbance . I then said goodbye to Actemra forever. This is the only negative report we have received.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who might benefit more: 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.

	e) People who exhibit raised levels of IL-6 in the blood after several months of treatment with GCs People who might benefit less: a) Patients who are experiencing a trouble-free tapering of steroids according to current BSR guidelines. b) Patients who experience intolerance to the technology.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We would argue that it would be highly inappropriate, and also discriminatory, for any consideration of mean age of patients to affect consideration of this technology for this condition. We would also consider it inequitable if a calculation of QALYs were severely affected by the demographic of the population at risk of GCA.
Other issues	
13. Are there any other issues that you would like the committee to consider?	We understand that TCZ would have to be prescribed and administered under the care of a consultant (probably a rheumatologist). We would consider this a very positive thing as there is evidence that, following initial diagnosis, significant numbers of patients are managed exclusively within primary care. We consider this to be inappropriate.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • GCA is an extremely unpleasant, serious and risky disease which carries the risk of damage to sight • Many patients are on steroids for years and are unable to reduce below a 'maintenance' dose • Long term steroid treatment is unsuitable for many older people who already have multiple co-morbidities • The challenge of tapering and coming off steroids is a major preoccupation for many patients – often considered as bad as, or worse than, the disease itself • TCZ treats the underlying cause of the inflammation of GCA, rather than masking the symptoms.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Tocilizumab for treating giant cell arteritis [ID1051]

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]; [redacted]
2. Name of organisation	**British Society for Rheumatology**
3. Job title or position	[redacted] **Dudley Group for Health NHS Foundation Trust, West Midlands;** [redacted] **University of Manchester** [redacted] **Norfolk and Norwich University Hospitals NHS Foundation Trust**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society for Rheumatology exists to promote excellence in the treatment of people with arthritis and musculoskeletal conditions and to support those delivering it. It is a professional association representing the whole multi-disciplinary team: consultant rheumatologists, trainees, specialised nurses, physiotherapists, occupational therapists, psychologists and GPs with special interest in rheumatology. The society aims to improve standards of care in rheumatology and secure a high priority for rheumatology services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To control symptoms (primarily headaches, but also systemic symptoms, such as fever, myalgia/ arthralgia, lethargy and fatigue), reduce inflammation and To reduce the risk of complications of the disease, i.e. visual loss, vascular events (stenosis or aneurysm) and that of treatment. Circa 80% of patients will suffer glucocorticoid toxicity and this treatment would be aimed at reducing the cumulative exposure of patients to glucocorticoids and thus reducing the risk and disabilities due to type 2 DM, weight gain, HT, CCF, easy bruising, osteoporosis etc.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Any 3 of the following 4: 1. Absence of constitutional symptoms 2. Absence of claudicant symptoms (including headache) 3. Normalisation of inflammatory markers (ESR < 30 mm/hr and CRP <10 mg/ l) 4. Normalisation of ultrasound halo We would expect the improvement within 4 weeks of diagnosis, and maintained at 12 month after diagnosis). Avoidance of new/ progressive complications attributable to active GCA. Finally: reduced treatment-related complications compared with current standard of care (SOC).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	High-dose steroids (minimum prednisolone of 40 mg daily orally along with intravenous methylprednisolone loading in some cases), tapering slowly over a minimum period of at least 24 months. Methotrexate is recommended as steroid-sparing agents in refractory/relapsing cases.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR and BHPR guidelines for the management of giant cell arteritis. 2010. https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/keq039a. (an update of these guidance is expected later this year) EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009 Mar;68(3):318-23. doi: 10.1136/ard.2008.088351. Epub 2008 Apr 15.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No – there is no debate about the need for corticosteroid treatment and the need for doses above 40 mg od loading. But the reduction regimens vary widely. The follow up arrangement vary widely. Variations exist regarding the use/ evidence in favour of steroid-sparing agents such as methotrexate, azathioprine or leflunomide. The BSR/BHPR guidance is currently under review, but the changes are likely to affect the diagnostic – rather than treatment – arm of the pathway. There is almost no guidance on treatment of refractory patients – the group of patients most likely to benefit from this drug.
• What impact would the technology have on the current pathway of care?	A key potential impact of this technology would be at diagnosis of GCA for those patients with current contraindications/intolerance to corticosteroid treatments – type 2 DM, CCF, steroid psychosis etc. The greatest impact is probably going to be for patients whose disease relapses on doses >15 mg pred or those who are suffering with significant complication of corticosteroid treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No - currently the technology is only available via individual funding request or via clinical trial- participation. We envisage that this will be used in the same setting as NHS England specialist centres/networks use biologic treatments for SLE, AAV etc.
• How does healthcare resource use differ between the technology and current care?	The technology is likely to require once weekly subcutaneous injections which after training can usually be mastered by the patient or a relative. The reduce steroid-exposure can be expected to lead to a reduced use of healthcare resources through reduced consultation, investigations and treatment rates and costs for complications of steroid exposure (uncontrolled diabetes mellitus, progressive osteoporosis/ osteoporotic

	fractures, neuropsychiatric symptoms, cataract formation, arterial hypertension). An increase of serious infections through the technology compared with current standard of care is presently not suggested.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment initiation and monitoring will be in secondary care, in those patients unable to self-inject, monthly intravenous administration of the treatment would be an alternative, but this would attract higher drug administration costs.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The treatment of the technology is available already as intravenous treatment (via NICE TAG) for rheumatoid arthritis, therefore most secondary care Rheumatology departments are set up to its use in principle. Pathways adjusted to the use in GCA will need to be agreed locally and training of patients/ carers in the safe administration of the technology involving primary/ secondary care (and home care providers) only where patient or carers are unable to perform the administration. There are already specialist centres and networks approved for looking after patients with vasculitis. The approval of the use of Toc could be through those existing structures.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, without any doubt.
• Do you expect the technology to increase length of life more than current care?	This remains to be proven in clinical/observational trials but in our opinion – yes.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	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. Patients with normal CRP may not be benefited.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Performing subcutaneous injections compared with oral medication (as this technology implies) represents usually an initial hurdle for patients to overcome, but the experience from related technologies of subcutaneous treatment in e.g. rheumatoid arthritis , suggests, the majority of patients and carers are perfectly capable of mastering this step. The technology may lead to patients lipid profile deteriorating to the point that lipid-lowering treatment with a statin may be necessary. But current treatment with prednisolone is already altering the lipid profile and increasing the cardiovascular and cerebrovascular risk.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules of starting treatment with the technology will be determined by the resulting NICE recommendation as well as the absence of recognised contra-indications of the existing technology as per British National Formulary and the manufacturer's summary of product characteristics. This will include assessment for Tb risk (history, chest radiograph , +/- interferon-gamma-release- based Tb reactivity test). Monitoring blood tests will be monthly for the first three months and 2-3-monthly thereafter and are unlikely to exceed what is reasonable for disease monitoring of this condition anyway. Intercurrent infections, reduction in peripheral blood white cell counts or platelets and newly emergent contra-indications to the treatment will lead to either a temporary or permanent stop of the treatment.

	We envisage the need for specialist input for monitoring these patients – including the use of ultrasonography.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Some of the benefits (e.g. cumulative steroid exposure resulting in reduced future risk of fracture, diabetic complications and cataract) may not be captured in health-related quality-of-life based calculations of QALY, as the risk reduction is long-term (ie beyond a year) and difficult to capture in clinical studies. It is difficult to prove that an event would have happened if it does not happen in an individual.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is both innovative for this indication and has the potential to make a significant and substantial impact on health-related benefits. This is the first real advance in the management of giant cell arteritis since 1955.
• Is the technology a 'step-change' in the management of the condition?	Yes, without any doubt.
• Does the use of the technology address any particular unmet need of the patient population?	The unmet need addressed by the technology is the reduction of short- and long-term steroid-related side effects, especially in patients who are relatively refractory in the disease to steroids.
17. How do any side effects or adverse effects of the technology affect the	Main concerns relate to risk of infection, side effects on full blood count, liver function and lipid profile.

management of the condition and the patient's quality of life?	The published randomised trial data so far suggests that the overall incidence adverse effects relating to the technology is not significantly different to the current SOC. We would favour that NICE approval includes a recommendation for post-marketing surveillance via a consent-based, industry-sponsored but BSR-owned register of patients undergoing treatment with this technology.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The *comparator* arm of available trials reflects current standard of clinical practice in the UK – albeit in an accelerated regimen of corticosteroid reduction. The technology is currently not licensed or available in standard UK practice, but we are aware that it received approval by the US Food and Drug Administration (FDA) in May 2017 (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm559791.htm?platform=hootsuite); accessed 5 July 2017). *Subcutaneous* tocilizumab in GCA: Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, Brouwer E, Cid MC,Dasgupta B, Rech J, Salvarani C, Spiera RF, Unizony SH, Collinson N. Efficacy and Safety of Tocilizumab in Patients with Giant Cell Arteritis: Primary and Secondary Outcomes from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/efficacy-and-safety-of-tocilizumab-inpatients-with-giant-cell-arteritis-primary-and-secondary-outcomes-from-a-phase-3-randomized-double-blind-placebo-controlled-trial/ Related Protocol description (describing intervention and control treatment arm): Unizony SH, Dasgupta B, Fisheleva E, Rowell L, Schett G, Spiera R, Zwerina J, Harari O, Stone JH. Design of the tocilizumab in giant cell arteritis trial. Int J Rheumatol. 2013;2013:912562. doi: 10.1155/2013/912562. Epub 2013 Apr 7. *Intra-venous* tocilizumab:

	Villiger PM, Adler S2, Kuchen S, Wermelinger F, Dan D, Fiege V, Bütikofer L, Seitz M, Reichenbach S.Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016 May 7;387(10031):1921-7.
• If not, how could the results be extrapolated to the UK setting?	Clinical trials will never use the same corticosteroid regimen as used in real life. Longitudinal studies demonstrate the need for 2 years of prednisolone reduction. This is not feasible in clinical trials. The extrapolation is through recognition of the superiority over corticosteroid regimens and restricting use for patients who relapse with current standard of treatment or have disease refractory to current treatment. I would not suggest using it first line as for patients in clinical trials.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Remission and relapse rates of GCA, as measured in the trials. Other important outcomes are as per Final Scope relating to this TA (June 2017), ie. The outcome measures to be considered include: disease remission, time to relapse after disease remission, adverse effects of long term corticosteroid treatment (including weight gain, osteoporotic fractures and diabetes mellitus); morbidity (including vision loss, stroke and aortic aneurysm); mortality; adverse effects of treatment; health-related quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not as far as we are aware. The peer-reviewed publication of the pivotal GiACTA trial (see Stone JH et al, 2016, as referenced under 18) will be crucial to allow firmer conclusions on adverse effect profile and efficacy data related to the technology.
19. Are you aware of any relevant evidence that might	We are not aware of any existing systematic reviews of trial evidence.

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No previous TA available on this technology.
21. How do data on real-world experience compare with the trial data?	There is currently no meaningful real-world data available. Personal data suggests that the majority of patients complete a 2 year course of prednisolone without relapsing.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	As per equality-impact-final scope (June 2017): The committee should ensure recommendations which apply equally regardless of age, so a difference in disease prevalence by age does not in itself represent an equality issue. The committee should also consider whether its recommendations could have a differential impact on people with conditions which pre-dispose them to sight loss.
22b. Consider whether these issues are different from issues with current care and why.	They are not.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- This the first targeted treatment in giant cell arteritis.
- This technology represent a new paradigm of treatment for this condition – the first meaningful change since 1955
- In particular for patients with GCA at high-risk of complications relating to the disease and/ or current SOC (high-dose steroids).
- It is the first ever treatment option for patients with relapsing and refractory disease.
- It will improve health-related quality of life and reduce steroid-exposure and as a consequence, steroid-related adverse events.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tocilizumab for treating giant cell arteritis [ID1051]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Justin Mason**
2. Name of organisation	**Imperial College London and Imperial College Healthcare NHS Trust**

3. Job title or position	**Professor of Vascular Rheumatology and Honorary Consultant Rheumatologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The ultimate treatment aims are to: • Induce disease remission • Maintain remission • Prevent complications including blindness and stroke and then move to the gradual treatment withdrawal. • This is predicated upon achieving a dosing regimen of corticosteroids with an acceptable side-effect burden.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Resolution of symptoms and return of the acute phase response markers (ESR, CRP, Hb, platelets, albumin) to the normal range with maintenance of this state on a dose of prednisolone of 7.5mg daily or less.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there is an urgent need for novel therapies in GCA. The side-effects associated with corticosteroids are unacceptable with 86% of patients experiencing long-term significant toxicity. In addition to the burden on patients, this has a substantial effect on healthcare resources. For example regular GP and hospital appointments, increased frequency and risk of infection, treatment of diabetes, treatment of hypertension and hospital admission for osteoporotic fractures, etc
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The mainstay of treatment is corticosteroid therapy starting at 40-60 mg daily and then tapering. In those who relapse during tapering, the dose of corticosteroid is increased to regain remission and then tapering begins again. This often leads to repeated increases in steroid therapy and a high cumulative dose. The latter is associated with a significant increase in serious side-effects. In those that partially respond or fail to achieve disease control on less than 7.5-10 mg prednisolone per day an immunosuppressive drug is often added (methotrexate, mycophenolate, azathioprine or leflunomide). The aim is to achive both disease remission and a steroid-sparing effect. The above approach is also considered for those at high risk of steroid side-effects eg. pre-existing hypertension, osteoporosis or diabetes and those presenting with large-vessel GCA and intense aortic uptake on an FDG-PET scan who are at risk of aortic aneurysm.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Society of Rheumatology guidelines 2010 (updated version currently under revision). EULAR guidelines for large vessel vasculitis 2009.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is generally well-defined. Due to the type of cases referred to ophthalmology and the increased risk of blindness, typically a higher starting dose of corticosteroid is used. Key differences are access to a fast track diagnostic service. Provision is patchy across the UK. Opinion varies on the efficacy of second line immunosuppressive agents due to the lack of robust clinical trial data.

• What impact would the technology have on the current pathway of care?	This would be the first drug with double-blind placebo-controlled trial evidence for significant efficacy in GCA. Amazingly, the first advance therapeutic advance in this condition since the 1950's. Impact would be seen particularly in those patients considered at high risk of corticosteroid side-effects and those in whom the disease recurrently relapses and is not controlled by low-dose prednisolone.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be an addition to the current care paradigm.
• How does healthcare resource use differ between the technology and current care?	Tocilizumab would be administered by the patient or carer as a s/c injection with therapy delivered to them at home, analogous to the use of many biologics for rheumatoid arthritis RA. Biologic therapy would require nurse specialist input initially for patient education and training. Given the average age of GCA patients, the number of patients living alone and unable to administer a subcutaneous injection to themselves is a consideration and may lead to further resource demand.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The drug should be prescribed in secondary care and ultimately administered by the patient and carer at home. Follow-up would involve shared care between a GP and a rheumatologist. Consideration might be given, at least initially, for advice to be sought from a specialist vasculitis clinic at least by telephone with respect to starting therapy. However, rheumatologists are now very experienced in the use of biologics across a range of different conditions and I don't see this being a long term requirement.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most rheumatology clinics are well set up for the administration of biologic therapies (prescription, training, monitoring). These biologics include tocilizumab and I envisage this indication will largely fit within that resource. However, introduction in GCA will impact on the biologic budget as a whole and additional funding would be required to cover that.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The clinical trial data suggest that tocilizumab will increase steroid-free remission rates and reduce cumulative steroid doses. Although the data is not yet available, if this steroid-sparing effect is sustained then I anticipate a marked reduction in long-term steroid-related toxicity.
• Do you expect the technology to increase length of life more than current care?	This is difficult to assess as GCA *per se* has not been shown to shorten life span. Undoubtedly in some patients life span is shortened as a consequence of steroid-related side effects but the impact of tocilizumab will be hard to measure.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. The impact of corticosteroids on the quality of life is very substantial and these have been outlined clearly by the patient organisations in the scoping matrix and I will not list them again. Thus, if the benefits of tocilizumab with respect to steroid-sparing are maintained, then this burden will be reduced. In addition, tocilizumab is likely to impact the profound tiredness and lethargy associated with the disease which impacts on quality of life. Similarly, the use of tocilizumab may reduce the total length of treatment required but again this remains to be established,

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I would initially recommend use in the following groups: 1. Those with refractory disease that cannot be managed with a dose of prednisolone of 7.5 mg daily or less. 2. Those considered at high risk of corticosteroid toxicity.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In contrast to current oral therapies, tocilizumab would be administered by the patient or carer as a s/c injection with therapy delivered to them at home. This would require nurse specialist input initially for patient education and training. Given the average age of GCA patients the number of patients living alone and unable to administer the medication is a consideration and may lead to further resource demand. Blood test monitoring is likely to increase in frequency somewhat but not in scope. This could be managed predominantly in primary care in most areas.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is an important and open question. As yet we have no guidelines or evidence as to when tocilizumab treatment could be withdrawn. One might envisage an 18-24 month treatment period before withdrawal. However, it should be noted that in the anecdotal cases reported, relapse rates following tocilizumab withdrawal were high. Drug-induced side-effects requiring cessation of therapy would be the same as those for the use of this drug in rheumatoid arthritis.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In my view there is a risk that the very significant long-term impact on the patient and costs to the health service of cumulative steroid toxicity will not be captured adequately in the QALY calculation.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	By definition this drug is innovative for the treatment of GCA being the only agent for whom controlled clinical trial data is available. Although the evidence is yet to be obtained, extrapolation of the phase II and phase III data on the reduction of cumulative steroid burden would suggest that there will be significant health benefits, particularly for those in whom steroid therapy confers a significant added risk or in those in whom steroid therapy is inadequate.

improve the way that current need is met?	Longer term impacts might include the potential for disease 'cure', better control of aortic disease in those with large vessel GCA and hence reduced risk of aortic dilatation, efficacy in those considered at high risk of visual loss. However, I must emphasise that data is lacking in all these areas.
• Is the technology a 'step-change' in the management of the condition?	Yes without doubt.
• Does the use of the technology address any particular unmet need of the patient population?	Yes it meets the main unmet need and that is an effective steroid-sparing therapy.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The trial evidence suggests that serious side-effects are rare and equivalent in the tocilizumab and placebo-controlled groups. This is similar to findings in the rheumatoid trials. There is a slight increased risk of serious infection and masking of associated symptoms due to suppression of the acute phase response.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	In the main yes. They do use a rather rapid steroid-tapering regimen which increases the rate of relapse in the placebo group. However, experience of previous failed trials suggests this approach is necessary to avoid masking of benefit by high dose prednisolone.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Disease remission. Yes 2. Disease-related morbidity. Yes 3. Long-term steroid-induced side-effects and morbidity. No 4. Time to flare. Yes 5. Quality of life. Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Reduction in cumulative steroid dose was measured at one year and this is likely to be indicative of reduced long-term steroid-induced morbidity but is not sufficient.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

23. How do data on real-world experience compare with the trial data?	There is very little real-world evidence due to lack of funding for the drug for this condition. However, the clinical trial data that is now available support the observations made in the retrospective studies reported.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No these have all been covered in the equality impact assessment
25b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- First substantial positive placebo-controlled clinical trial data for a drug in the treatment of GCA.
- Addition of tocilizumab increases rate of steroid-free remission and reduces cumulative steroid burden at 52 weeks.
- Tocilizumab should be considered initially in GCA for those considered at high risk from corticosteroid therapy or those requiring inappropriate doses to maintain remission.
- Use of tocilizumab is already safely established in RA clinical practice and in GCA the side-effect profile appears to be comparable and was equivalent to the placebo group.
- Long-term data is required to demonstrate a benefit of tocilizumab on steroid-related morbidity and to guide treatment reduction/withdrawal.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tocilizumab for treating giant cell arteritis [ID1051]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Miss Susan P Mollan**
2. Name of organisation	**Royal College of Ophthalmologists**

3. Job title or position	**Consultant Ophthalmologist**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it x other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat the condition and prevent relapses.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Conventional treatment is a long-term Glucocorticoid (steroid) taper over 1.5 years to 2 years with many remaining on low dose steroids for many years. A significant treatment response would be signs and symptoms free without clinical flare and without the continual use of steroids. A total reduction in overall steroid cumulative dose is essential.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Reduction in Glucocorticoid cumulative dosing and targeted treatment is without a doubt the unmet need in Giant Cell Arteritis.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	High dose oral glucocorticoids (GC) with dose tailored to symptoms and signs usually occurs over 1.5-2 years, with many remaining on GC long-term. For patients with ischaemic symptoms, such as sight loss, high dose intravenous methylprednisolone followed by high dose oral taper of GC, typically over 1.5-2 years, with many remaining on steroids long-term. Those within rheumatology services, and those with co-morbid conditions such as cardiac disease or diabetes are switched to a steroid sparing agent such as methotrexate.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	All recommend initiating high-dose GC treatment immediately if giant cell arteritis is suspected. 1. Guidelines from the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) [Dasgupta et al, 2010: Dasgupta, B., Borg, F.A., Hassan, N. et al. (2010b) BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology***49**(8), 1594-1597.] 2. European League Against Rheumatism (EULAR) [Mukhtyar et al, 2009: Mukhtyar, C., Guillevin, L., Cid, M.C. et al. (2009) EULAR Recommendations for the management of large vessel vasculitis.*Annals of the Rheumatic Diseases***68**(3), 318-323] 3. NICE CKS: Giant Cell Arteritis (July 2014) last accessed 28th August 2017 at https://cks.nice.org.uk/giant-cell-arteritis#!topicsummary)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway of care is not as clear as this condition presents to many different health care professionals from Rheumatologists, Ophthalmologists, A&E doctors, General Practice, Neurology and other specialities (ENT, GI, dentistry etc). The majority of patients are managed long-term under Rheumatology, General Practice and Ophthalmology. Other specialities may have a smaller number of patients such as Neurology.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The impact of this technology would move the condition to be more exclusively under Rheumatology, and those with a specialist interest in immunosuppression. This move would be welcomed, there are a number of unmet needs of these patients with patients suspect with GCA. These are: 1. Under diagnosis, over diagnosis and late diagnosis; 2. Glucocorticoid morbidity or toxicity, in particularly as treatment can be continued long-term without review by those who do not have up to date experience of the disease.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I would assume that high dose GC would be used whilst the patient is being diagnosed and confirmed as having the condition, then tocilizumab would then be started and the GC tapered immediately.
• How does healthcare resource use differ between the technology and current care?	At face value the technology will be perceived as high resource, and GC as low cost. However the side effects of GC induced diabetes, fractures and other morbidities should be included in the health economics debate of introducing this technology to the NHS.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care would be a safe environment for the technology, particularly in those clinics with special set-up for immunosuppression initiation and monitoring.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most rheumatology services already use the technology for Rheumatoid Arthritis, so I assume very little investment would be required to introduce the technology.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The GiACTA study (NCT01791153) is the Phase III, global, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of tocilizumab as a novel treatment for GCA did demonstrate clinically meaningful benefits, of reduced cumulative steroid doses, reduced time to first flare and remission. [Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, Brouwer E, Cid MC, Dasgupta B, Rech J, Salvarani C, Schett G, Schulze-Koops H, Spiera R, Unizony SH, Collinson N. Trial of Tocilizumab in Giant-Cell Arteritis.N Engl J Med. 2017 Jul 27;377(4):317-328.]
• Do you expect the technology to increase length of life more than current care?	The literature suggests that GCA co-morbidities of treatment do not shorten life, but significantly reduces quality of life. I do not think it will prolong the life expectancy of the majority of who suffer with GCA. However there is a small portion of those who present late with devastating disease, and the technology could lengthen those patient's life expectancy.
• Do you expect the technology to increase health-related quality of life more than current care?	I expect the technology to improve the quality of patient's lives compared to conventional GC treatment. Short term side-effects of GC treatment can significantly alter patients' mood, sleep habits, cause depression, fatigue and rarely cause psychosis, which is not a feature of the technology. The longer-term GC toxicity which includes diabetes, weight gain, fractures (the majority being vertebral and hip fractures), cataracts and glaucoma.
13. Are there any groups of people for whom the technology would be more or	I believe this will be effective in new onset disease and relapsing GCA.

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For patients they will have to learn to perform the subcutaneous injections on a weekly basis. However, in comparison to managing a tapering steroid dose where individual tablets need to be counted out on a daily basis, I do wonder whether patients will find a once weekly dose more appealing. At initiation and long-term, bloods such as full blood count and liver functions need to be tested. However, this would be in the normal clinical setting of having to be managed any way. The one thing patients and clinicians would need to be aware of, is that the technology changes the acute phase response, and hence if the patient was unwell, such as a chest infection or urinary tract infection, they would need to relay on their symptoms rather than their acute phase bloods.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	The clinician may want to check the Hep B status of the patient prior to starting treatment.

Do these include any additional testing?	At 1-2 months following first injection: Full blood count (FBC), liver function tests (LFTs), and serum cholesterol. Every three months: FBC and LFTs. Every six months: Serum cholesterol.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am uncertain that I am qualified to answer this question. QALY is one measure of outcome, but there are many others.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology is currently the only targeted treatment for GCA with a phase three trial evidence to support its use in GCA. It will improve the long-term health of these patients, compared to the current standard of care with glucocorticoid treatment.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, absolutely.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, targeted therapy.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The common side-effects are: upper respiratory tract infections (common cold, sinus infections); headache; increased blood pressure (hypertension) and injection site reactions. Rarer complications can include ulcer perforations, serious allergic reactions. Compared to GC short, medium and long-term side-effects, the side effect profile of the technology may be deemed to be much better for the patient and their quality of life.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Actually the clinical trial had a very steep GC taper, that we would not typically do in UK (or elsewhere), but it clearly shows the steroid sparing effect of TCZ in its results.

• If not, how could the results be extrapolated to the UK setting?	It shows us that with the technology we could be very aggressive at reducing the GC, and hence preventing GC side-effects and long-term toxicity.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, time to first flare of the disease and cumulative steroid dose. These were both measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No this technology has been used successfully in Rheumatoid Arthritis for many years and the side-effect profile is well known and well tolerated.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

23. How do data on real-world experience compare with the trial data?	Most of the case series have used this in refractory patients, with good benefit.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	One consideration is this is a disease of older people. Elderly people can be at risk of discrimination.
25b. Consider whether these issues are different from issues with current care and why.	None that I am aware of.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Tocilizumab (TCZ) is a game changer in the treatment of Giant cell Arteritis.
- The evidence is the largest trial ever conducted in GCA, which was rigorous and showed the superior benefit of TCZ compared to GC alone.
- IL-6 inhibition through TCZ, is a targeted therapy that has a known tolerable side effect profile.
- Current treatment with Glucorticoids alone has a hidden cost to the healthcare system.
- Current treatment with Glucorticoids alone has a hidden cost to the quality of life of our patients with Giant cell Arteritis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group's Report
Tocilizumab for treating giant cell arteritis

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
AFT	Accelerated failure time
ALT	Alanine transaminase
ACT	Aspartate transaminase
AESI	Adverse events of special interest
BHPR	British Health Professionals in Rheumatology
BSR	British Society for Rheumatology
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
CUA	Cost utility analysis
DH	Department of Health
DSU	Decision Support Unit
EE	Economic evaluations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQoL 5 Dimensions questionnaire
EQ-VAS	EuroQoL visual analogue scale
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	(US) Food and Drug Administration
FTP	Fast Track Pathway
FU	Follow-up
GC	Glucocorticoid
GCA	Giant Cell Arteritis
HCRU	Healthcare Resource Utilisation
HE&OR	Health Economics and Outcomes Research
HIRU	Health Information Research Unit

HR	Hazard ratio
HRQL	Health-related quality of fife
HSUV	Health-state utility values
HTA	Health Technology Assessment
HUI	Health utility index
ICD-9-CM	International Classification of Diseases, Clinical Modification
ICER	Incremental cost-effectiveness ratio
Incr	Incremental
IQR	Interquartile range
ITT	Intention-to-treat
IU	International Units
IV	Intravenous
IVRS	Interactive Voice-Response System
KM	Kaplan-Meier
LTFU	Long-term follow-up
LSM	Least square means
LV	Large vessel
LYG	Life years gained
MCDA	Multi criteria decision analysis
MCS	Mental Component Score
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
MR	Magnetic resonance
MRU	Medical Resource Utilisation
MTX	Methotrexate
NA	Not applicable
NE	Not evaluable
NHS	National Health Service
NHS EED	NHS Evidence Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
NS	Not significant
OCS	Oral corticosteroids
OLE	Open-label extension
ONS	Office for National Statistics
P	p-value
PAS	Patient access scheme

PASLU	Patient access scheme liaison unit
PBO	Placebo
PBO +26	Placebo plus a 26 week glucocorticoid taper
PBO + 52	Placebo plus a 52 week glucocorticoid taper
PCS	Physical Component Score
PFC	Points for clarification
PGA	Patient global assessment
PH	Proportional hazards
PIM	Promising Innovative Medicine
PK	Pharmacokinetics
PMR	Polymyalgia rheumatica
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PY	Patient years
QALY	Quality-adjusted life years
QW	Once per week
Q2W	Once every other week
RCT	Randomised, controlled trial
RA	Rheumatoid arthiritis
SAE	Serious adverse events
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Short Form
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMQN	Standardised MedDRA Query, narrow (scope)
SOC	System organ class
STA	Single technology appraisal
TAB	Temporal artery biopsy
TB	Tuberculosis
TCZ	Tocilizumab
TCZ QW +26	Tocilizumab once a week plus a 26 week glucocorticoid taper

TCZ Q2W +26	Tocilizumab twice a week plus a 26 week glucocorticoid taper
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TTFF	Time to first flare
TTO	Time trade off
UK	United Kingdom
ULN	Upper limit of normal
US	Ultra sound
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WHO	World Health Organisation

1 Summary

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

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

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

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

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

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

once a week (QW) dosing and one every other week (Q2W) dosing; only the once a week dosing is licensed and therefore, this report presents tocilizumab results for this dose only. The GC taper used alongside tocilizumab lasts 26 weeks. The ERG notes that this is much shorter than the length of GC taper used in current clinical practice (see further discussion of this below). Although it is likely that a 26 week taper would be attempted with tocilizumab in practice, with the aim of gaining the potential steroid sparing benefits of tocilizumab, it is not certain how generally this would be achieved.

The comparator for this submission was established clinical management without tocilizumab. The comparator used in the GiACTA trial was placebo with either a short (26 weeks) or long (52 weeks) prednisone taper regimen according to a defined schedule. This matched the NICE scope. The CS clarified that prednisone/prednisolone was used as it is the mainstay of treatment for people with GCA; published evidence and clinical advice to the ERG confirmed that in the NHS prednisolone is used rather than prednisone. The ERG notes that prednisolone and prednisone are highly comparable drugs, prednisone being the metabolic precursor of prednisolone. The GiACTA trial used two different placebo controls: one with a 26 week GC taper and one with a 52 week taper. The ERG notes that the BSR recommends a GC tapering regimen which adds up to a minimum of 52 weeks and a cumulative GC dose between 3.6g and 7.4g over approximately 1 - 1.5 years, in those patients who do not experience a relapse or flare. Therefore, the placebo+52 week GC taper is the more relevant comparator for UK clinical practice.

The outcomes measures for the submission were: disease remission, time to relapse after disease remission, GC exposure, adverse effects of treatment and health-related quality of life. These essentially matched the outcomes listed in the NICE scope. However, morbidity (including vision loss) was listed in the NICE scope as an outcome but vision loss was not reported in the CS as a separate outcome. After this issue was raised in the points for clarification, the company confirmed that vision loss was recorded as part of the clinical assessment for each patient at each study visit. The company pointed out that, "The level of clinical excellence employed by the investigators in monitoring disease activity ensured that any increase in disease activity was appropriately treated to prevent severe complications such as permanent vision loss." Therefore, the ERG agrees that vision loss is not an important trial outcome.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS presented two RCTs of tocilizumab in GCA: the Phase II study (NCT01450137) and a Phase III RCT (GiACTA). GiACTA is the only RCT that provides data on the effectiveness of the licensed dose of tocilizumab in patients with GCA. The Phase II study (NCT01450137) provides only supporting evidence. The CS stated it would not be appropriate to attempt pooling of the efficacy data from the Phase III GiACTA study and the Phase II NCT01450137 study because of differences in treatment regimens and study designs, therefore a standard meta-analysis was not feasible.

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

Sustained remission

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

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

Flare

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

Cumulative dose of GC

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

Sub-group analyses

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

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

The median time to GCA disease flare in new-onset GCA patients was 169 days in the PBO+26 group and was not calculable for the other three groups due to fewer than 50% of the new-onset patients in these groups experiencing a flare. In relapsing patients it was 165 days in the PBO+26 group and 274 days in the PBO+52 group but was not calculable in the tocilizumab treatment groups. The ERG analysed both subgroups and found that the relative treatment effect was slightly less in the new-onset patients (HR 0.44, 95% CI 0.29 -1.59; (p=0.004)) compared with the relapsing patients (HR 0.33, 95% CI 0.14 – 0.81; (p=0.04)

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

Health related quality of life

There was no notable deterioration observed in HRQL in any treatment group, however the tocilizumab groups appeared to score marginally better. The only statistically significant difference was seen for the SF-36 Physical Component Score. There was no substantial deterioration in the EQ-5D scores in any treatment group. Numerically higher mean changes in the FACIT-F from baseline were observed for the tocilizumab treatment group versus the placebo group. However, no statistical testing was performed. Both, the TCZ QW+26 and PBO+52 groups showed a numerical improvement from baseline in the Mental Component Score; however there was no significant difference. Therefore, there is limited evidence to indicate that HRQL improves substantially with tocilizumab compared to placebo.

Adverse effects of tocilizumab

The safety profile of tocilizumab appears to be similar to the placebo used in the trial. The total number of patients with at least one AE was similar across all treatment groups; however it was highest in the TCZ-QW group (98.0%) and lowest in the PBO+52-week group (92.2%). Furthermore, there were a higher number of patients experiencing infections in the TCZ QW+26 group (75%) compared with the PBO+52 group (64.7%) (Table 22, Page 64 of the CS). As tocilizumab is given with the intention of being steroid sparing it might be hoped that GC-associated AEs would be lower in the TCZ QW+26 arm. In GiACTA however, the percentage of patients reporting an AE considered related to GC use by the investigator was similar in the TCZ QW+26 (50%) and PBO+52 (49%) groups.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The GiACTA trial was a large, relatively good quality, double-blinded, RCT. However, there were some prognostic factors which were unbalanced between the four arms in the GiACTA trial: these imbalances may slightly reduce the reliability of the study results. In addition, the primary outcome of

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

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

- The number of patients from the UK in the TCZ QW+26 arm of the trial was only 7.
- The GiACTA trial includes both new-onset and relapsing GCA patients. Clinical advice to the ERG indicated that these two subgroups of patients would be treated differently in practice. The analysis of the GIACTA trial can be criticised because it did not take into account the difference between new-onset and relapsing patients, nor that between those who were in remission at baseline and those who were not. Randomisation was stratified by baseline prednisone dose only. Whilst there was a significant difference in baseline prednisone dose between new-onset and relapsing patients, this stratification will not account for the other differences between the new-onset and relapsing populations. Sub-group analyses by disease status at baseline (new-onset or relapsing) for sustained remission at week 52, for time to GCA flare, and cumulative GC dose were reported in the CS.
- The baseline characteristics of the GiACTA population appear to be fairly representative of the UK GCA population. However, the ERG notes that there is a difference in the mean age of patients in the GiACTA trial (69.05 years) and that from the UK CPRD data source (73 years). Also, overall there was a higher ratio of large vessel GCA patients to cranial GCA patients than would be seen in NHS practice.
- The trial uses a 26 week GC taper for three of the four treatment groups. The tapering regimen recommended by BSR adds up to a minimum of 52 weeks. Hence, the placebo arm with a 52 week GC taper is most relevant to UK clinical practice. The 26 week taper used with tocilizumab is likely to be attempted in clinical practice, with the aim of reducing the GC load.
- Although the trial included four treatment arms the only comparison relevant to NHS practice is that between TCZ+26 and PBO+52

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness of tocilizumab for GCA and a separate model. The review identified a single previously

published study that assessed the lifetime costs and consequences of two tocilizumab doses (TCZ QW and TCZ Q2W) in combination with a 26 week prednisone taper regimen compared to a 52 week prednisone taper regimen alone. The published study shares an identical structure and many common inputs and assumptions to the company model. The ERG considered that the cost-effectiveness analysis reported in the company model to be the most relevant source of evidence to inform the decision problem.

The company submission was based on a semi-Markov model using a weekly cycle length. The model evaluated the lifetime (30-years) cost-effectiveness of tocilizumab in combination with a 26-week prednisone taper regimen compared to a 52-week prednisone taper regimen alone. The model used GiACTA trial data to estimate the impact of tocilizumab on disease control (e.g. time in remission and number of flares) and real world data to estimate the effect of steroid sparing. The real world data was used to quantify the relationship between cumulative prednisone dose and the risk of steroid related adverse events in GCA patients.

The model included seven separate health states: (i) On remission and on steroid; (ii) On remission and off steroid; (iii) On relapse/flare; (iv) On remission and on maintenance steroids (escape); (v) GCA-related complications; (vi) Steroid-related AEs and (vii) Death.

Separate remission states were used before and after a first flare to account for different transition probabilities and glucocorticoid (GC) exposure based on GiACTA trial data. GCA-related complications (vision loss and stroke) were assumed to only occur from the relapse/flare state and transitions were derived from external literature. Steroid-related AEs included fractures and diabetes based on cumulative GC dose and evidence from real world data. Death included background mortality (general population, age and gender matches) arising from any state with an adjustment for stroke related mortality attributed to GCA-related complications

Treatment with tocilizumab was assumed to be continued over a 2-year fixed treatment period in the base-case analysis .This was justified by the company based on the CHMP Positive Opinion which states that tocilizumab can be continued beyond 1-year, clinical opinion and the typical duration of conventional treatment for GCA with GCs. The 52-week GC tapering regimen included in the GiACTA trial was considered an appropriate comparator and consistent with the most rapid GC tapering regimen recommended in clinical guidelines.

Transition probabilities from the initial remission state to the first flare/relapse event were based on individually fitted parametric models using patient-level data from the ITT population of the GiACTA trial. Transition probabilities from the subsequent remission state to flare were based on a separate

Poisson regression. The effectiveness of tocilizumab was assumed to be maintained over a lifetime and justified by the company based on early results from open label data.

The risk of GCA related complications was assumed to be related to subsequent relapses/flares. In the absence of these complications arising in the GiACTA trial, estimates were sourced from a separate published economic model comparing alternative diagnostic approaches for GCA. The use of external evidence was justified by the company as these events are rare but associated with significant and potentially lifelong cost and health-related quality of life (HRQoL) implications.

Cumulative GC dose for each treatment arm were based on 3 separate estimates to reflect dosing during: (i) the initial remission period (prior to first flare), (ii) during secondary remission (post-initial flare) and (iii) during relapse/flare. Dose estimates were based on data from the GiACTA trial and real world data. Background mortality was derived from standard lifetables and justified based on findings from a systematic review which found no significant differences in mortality for GCA patients.

Utilities for the remission and relapse/flare states were sourced from a mixed effect regression model based on EQ-5D data from GiACTA. Data was combined across the separate arms given the lack of significant difference by treatment arm reported within the trial. The relapse/flare utility was applied for a 4-week duration based on published literature and clinical opinion. Utility decrements for GCA and GC-related complications were sourced from the external literature.

The treatment costs of tocilizumab and GC were based on published prices and the approved PAS scheme for tocilizumab. No additional administration costs were assumed for tocilizumab. The cost of conventional GC treatment was based on published prices for prednisone. Following points for clarification, the company altered the costs for conventional GC treatment using published prices for prednisolone which is more commonly used in the NHS. Health state costs were based on third-party market research undertaken by the company. The costs of GCA related complications and GC related AEs were derived from the external literature.

The company's base-case results were based on the overall ITT population. Separate results for the subgroups identified within the NICE scope (newly diagnosed and relapsed/refractory) were included in the company's response to the points for clarification. Only the results from the PAS analysis were considered by the ERG.

The company base-case deterministic ICER for tociluzumab treatment with GC versus GC alone for the ITT population was £28,272 per additional QALY. The subgroups ICER's were £37,334 per QALY in the newly diagnosed subgroup and £22,403 per QALY in the relapsed/refractory subgroup.

The disaggregated QALY data provided by the company showed that the main driver of incremental QALY gains was the additional time patients are assumed to be in one of the remission states with tocilizumab treatment. The QALY gains are derived from two main sources: (i) a longer time to first flare, which means that patients receive the higher utility of remission and avoid the utility decrement of GC-related AEs; (ii) fewer subsequent relapse/flare events. The impact of differences due to GCA-related complications was minor.

The disaggregated cost data indicated that the main driver of cost differences was the additional acquisition cost of tocilizumab treatment. These additional costs were partially offset by a lower disease management cost (i.e. longer time in the 'On remission and off steroid state) and reduced flare costs. Additional cost-offsets were assumed in terms of reduced GCA-complications and GC-related adverse events. However, these offsets appeared less significant than the disease management and flare costs.

The major driver of the differences in the ICER estimates across the populations was differences in the total number of flares. The incremental difference in the number of flares was estimated to be -5.87 in the newly diagnosed and -19.21 in the relapsed/refractory subgroups, compared to -12.24 in the base-case ITT population. The differences across the different populations were due to different parametric functions for the time to first flare and different rates of subsequent relapse/flare events.

The probabilistic base-case ICER reported by the company for the ITT population was £30,579 per QALY. The ERG was unable to replicate the company probabilistic ICER estimates.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's logical checks identified an important error in the QALY calculations which was corrected by the company and a revised model and full set of results were provided by the company. Although the ERG was satisfied with the internal validity of the revised model, significant concerns remained regarding the clinical and external validity of the longer-term extrapolations and the extent to which the company model appropriately represented the natural history of GCA.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical

The systematic review conducted to identify relevant trials used methods that were generally appropriate; it is unlikely that any relevant randomised controlled trial (RCT) of tocilizumab has been missed. The CS presented two RCTs of tocilizumab in GCA: the Phase II study (NCT01450137) and a Phase III RCT (GiACTA). GiACTA is a good quality RCT that provides data on the effectiveness

of the licensed dose of tocilizumab in patients with GCA. The Phase II study (NCT01450137) provides supporting evidence.

Cost-effectiveness

The company's economic submission met the requirements of the NICE reference case. The company submission acknowledged many of the key uncertainties and the cost-effectiveness model incorporated a range of scenario analyses that allowed the impact of alternative assumptions to be explored. The company provided a revised model and included subgroups within their response.

1.6.2 Weaknesses and areas of uncertainty

Clinical

The treatment effect in new-onset vs relapsing patients was not fully explored, nor was the effect in patients with GCA vs LV or both.

The generalisability of the trial is uncertain due to the age of patients, the ratio of cranial vs LV GCA patients, and the uncertainty regarding the taper that will be used with tocilizumab in practice

The available preliminary evidence indicates that around 30% of patients will flare once tocilizumab treatment is stopped: for sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients. Therefore, further reliable and accurate research is needed to determine the long term effectiveness of tocilizumab in maintaining remission in patients with GCA.

Cost-effectiveness

The ERG was concerned that the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration did not appear to be justifiable based on early results from the OLE study and the published results from the previous RCT. The external evidence identified by the ERG also raised uncertainties regarding the external validity of the longer-term predictions.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

A series of additional revisions and alternative assumptions were explored by the ERG using additional scenarios. These scenarios explored uncertainties related to: (i) the duration of treatment and the assumption that the benefits of tocilizumab continue over a lifetime; (ii) uncertainty concerning the choice of parametric survival models for time to first flare and use of different model types and (iii) uncertainty concerning the rate of subsequent relapse/flares following an initial flare. The ERG proposed alternative assumptions and data sources which they considered had greater face validity and were more consistent with the natural history of GCA reported in longer-term epidemiological studies. These alternative approaches and data sources were then combined as part of an alternative ERG base-case analysis.

The ERG's alternative base-case presented results for alternative treatment duration periods between 1 and 2 years. The ERG ICER results were higher than those reported by the company. The ERG probabilistic ICERs for a 1-year treatment period were: £36,960 (ITT population); £41,577 (newly diagnosed subgroup) and £30,158 (relapsed-refractory subgroup) per QALY. The ERG probabilistic ICERs for a 2-year treatment period were: £65,801(ITT population); £73,046 (newly diagnosed subgroup) and £58,411 (relapsed-refractory subgroup) per QALY.

The ERG considers that the 1-year treatment period results provide the most internally valid estimates consistent with the treatment duration period assessed in the GiACTA trial. However, in the absence of a clear stopping rule for tocilizumab there remains significant uncertainty concerning the appropriate duration of tocilizumab treatment. The differences reported between the company and ERG highlight that important uncertainties remain concerning the optimal duration of tocilizumab treatment and the associated longer-term benefits.

2 Background

2.1 Critique of company's description of underlying health problem

The relevant health problem in the present appraisal is Giant Cell Arteritis (GCA), which is an inflammatory vasculopathy affecting large and medium-sized arteries, primarily the extracranial branches of the carotid arteries and the aorta's primary branches. The company submission (CS) stated that GCA is a potentially life-threatening condition linked with substantial impairment of the day-to-day functioning of patients.[1] The ERG believes that describing GCA as a potentially life threatening condition is not well substantiated: whilst GCA may rarely lead to life threatening events such as aortic aneurysm rupture or stroke, at a population level there is no clear evidence that long-term mortality is significantly increased in patients with GCA compared to individuals without GCA.[2] The CS reports mortality as an outcome; however it is not the main concern for GCA patients.[1] Although, the overall life expectancy of patients with GCA is similar to that of the general population, GCA can increase the risk of developing serious problems, debilitating patients and reducing their quality of life.[3, 4] The greatest driver of treatment decisions, for many doctors and patients, is most likely the fear of visual loss balanced against awareness of the burden of glucocorticoid therapy.[5]

GCA is a rare condition, it is estimated that around 1 in every 4,500 people will develop it in the UK each year.[3] The CS stated that GCA primarily affects adults ≥50 years. The risk increases with age, with the highest rates being observed between 70 and 79 years.[6, 7] The ERG requested the UK incidences of GCA in people aged over 50 and 70 years old as the CS did not initially provide these. The CS response stated that Petri et al.[7] reported the incidence in women aged 70-79 years old as 7.4 per 10,000 person-years, with an estimate of 3.7 per 10,000 years in men. The CS stated that the incidence in men peaks at age 80, whereas in women it peaks at age 70 to 79 years. The ERG notes that GCA is three times more common in women than in men and seven times more common in white people than in black people[8]; this was not stated in the CS.

The CS describes two clinical subtypes of GCA: cranial GCA which is the most typical presentation; and large vessel GCA which is less common. Clinical advice to the ERG is that these are two manifestations of the same disease, and that with increasing use of vascular imaging these two clinical subtypes may often be seen together in the same patient. Cranial GCA involves the extracranial branches of the carotid arteries and can result in ischaemic manifestations such as severe headache, scalp tenderness and jaw claudication. Serious manifestations/complications of cranial GCA relate to vision; these range from transient diplopia to sudden, partial or complete vision loss. The serious complication of vision loss usually manifests before or shortly after diagnosis and once established it is almost always permanent, but it can be prevented with early treatment.[9] Clinical advice to the ERG indicates that once treatment is initiated and appropriately managed, it is rare for patients to develop vision loss. Approximately 20% of untreated GCA patients have manifestations of vision loss,

whereas permanent vision loss can affect approximately 12-15% of patients.[6, 9, 10] The CS states that approximately 30% of GCA patients experience visual manifestations, but the ERG notes that this figure does not apply to actual vision loss.

Large-vessel GCA (LV GCA) affects the aorta and its primary branches. The CS describes the complications of LV GCA as aortic aneurysms, aortic dissection[11] and coronary arteritis.[12] Compared to the general population, aortic aneurysms are 17 times more likely in GCA sufferers. Most patients with GCA will develop aortitis but it manifests clinically in approximately 15% of patients.[12] Clinical advice to the ERG indicated that patients with large vessel GCA tend to have longer disease duration with more relapses, whereas patients with cranial GCA generally have shorter disease duration of approximately one to two years with fewer relapses compared to those with LV-GCA. A study by Alba et al. reported that a relapsing GCA course is associated with higher and prolonged GC requirements[13]. For this reason, patients with large vessel GCA are typically harder to treat compared to patients with cranial GCA.

The CS states that in approximately 90% of patients the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) is elevated. However, clinical advice to the ERG puts this figure at 95% to 98%. Furthermore, CRP has been shown to be more effective in diagnosing GCA than ESR.[14]

Overall, the ERG believes that the CS generally presented appropriate and relevant information on the underlying health problem. However, the CS overstated the incidence of visual manifestations in patients with GCA and describing GCA as a life threatening condition was unsubstantiated.

2.2 Critique of company's overview of current service provision

The CS correctly stated that there are no NICE guidelines for GCA; however, the British Society for Rheumatology (BSR) has developed clinical practice guidelines to advise the diagnosis and management of GCA.[15] The BSR recommends immediate initiation of high-dose glucocorticoid (GC) treatment after suspicion of GCA to prevent sudden vision loss and other ischaemic complications. Diagnosis of GCA should be done using temporal artery biopsy, signs and symptoms of GCA and elevated CRP or ESR levels.

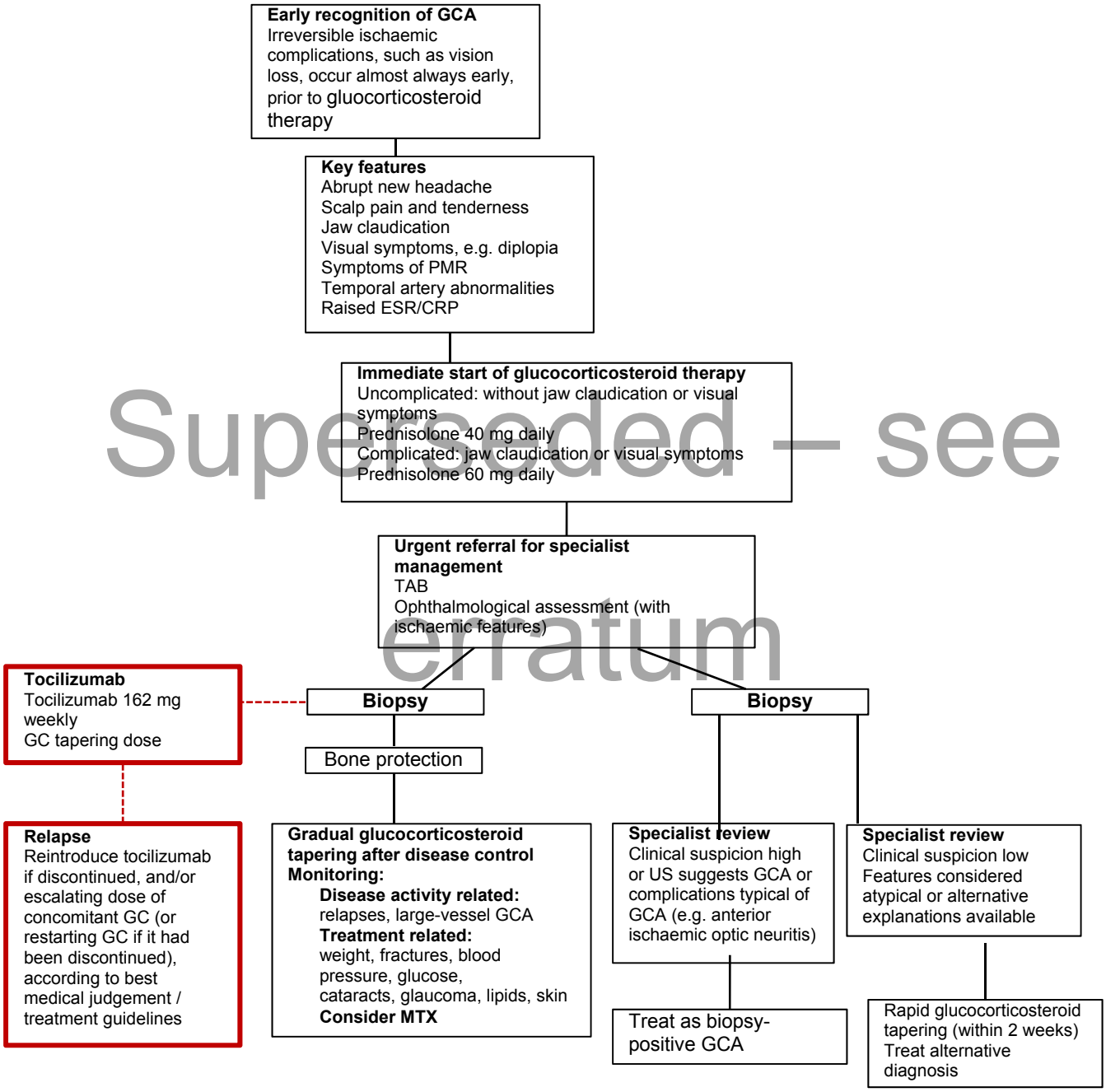
The CS reports that current treatment mainly consists of high dose GC (usually prednisone – the ERG notes that in the UK this is usually prednisolone) followed by long-term steroid tapering.[9, 16] Complicated GCA (evolving vision loss or established vision loss) is treated with an initial dose of 60mg or above, whereas uncomplicated GCA (No jaw or tongue claudication or visual symptoms) is treated with 40-60mg. Once signs and symptoms of GCA are absent patients are slowly tapered off GC. The ERG notes that the BSR recommends a GC tapering regimen which adds up to a minimum of 52 weeks and a cumulative GC dose between 3.6g and 7.4g over approximately 1 - 1.5 years, in

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

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

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

Figure 1 Typical treatment pathway for advanced/metastatic breast cancer (CS Figure 1 Page 24)



3 Critique of company's definition of decision problem

3.1 Population

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

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

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

3.2 Intervention

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

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

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

results for this dose only. The GC taper used alongside tocilizumab lasts 26 weeks. The ERG notes that this is much shorter than the length of taper used in clinical practice. The tapering regimen recommended by BSR adds up to a minimum of 52 weeks.[15] Clinical advice to the ERG indicated that, in practice, clinicians will aim to achieve this 52 week taper, but a sizeable proportion will flare, and the treatment/taper starts again. The average length of GC treatment is estimated at 2 years. However, clinical advice to the ERG is that in combination with tocilizumab clinicians will seek to taper GC more rapidly than 52 weeks, and quite possibly aim for a 26 week taper, in order to try to benefit from the GC sparing potential of tocilizumab.

The Phase II study (NCT01450137) tocilizumab was delivered by intravenous infusion: 8mg/kg every 4 weeks. This trial is therefore, not directly relevant to the NICE scope.

3.3 Comparators

The comparator presented by the CS was established clinical management without tocilizumab. The comparator used in the GiACTA trial was placebo with either a short (26 weeks) or long (52 weeks) prednisone taper regimen according to a defined schedule.

This matched the NICE scope. The CS clarified that prednisone was used as it is the mainstay of treatment for people with GCA, both in newly diagnosed (new-onset) and in relapsed/refractory GCA. Clinical advice to the ERG confirmed that in the NHS prednisolone is used rather than prednisone. Furthermore, a study of data from the UK-based Clinical Practice Research Datalink (CPRD) found that 99.7% of patients in the UK received prednisolone.[7]

The CS also confirmed in their response to the PFC that prednisolone is recommended in the GCA guidelines. However, the ERG notes that prednisolone and prednisone are highly comparable drugs, prednisone being the metabolic precursor of prednisolone.

The GiACTA trial used two different placebo controls: one with a 26 week GC taper and one with a 52 week taper. Therefore, based on the discussion of UK practice in Section 3.2 the placebo + 52 week GC taper is the more relevant to UK clinical practice, albeit still a little shorter than typically seen in practice.

The BSR also stated that immunosuppressant's such as methotrexate could be used as steroid-sparing agents when combined with GC. However, the CS did not include methotrexate as a comparator, stating that evidence for methotrexate as treatment of GCA is inconsistent. Clinical advice to the ERG confirmed that methotrexate is not effective in treating GCA and is poorly tolerated in older populations. Therefore, in practice it is mainly used as a co-treatment rather than a comparator.

Similarly, the phase II randomised, placebo-controlled study compared tocilizumab to a placebo comparator with a GC taper in both treatment arms.

3.4 Outcomes

The outcomes specified in the CS Decision Problem were:

- Disease remission
- Time to relapse after disease remission
- GC exposure
- Adverse effects of treatment
- Health-related quality of life

These essentially matched the outcomes listed in the NICE scope. However, morbidity (including vision loss) was listed in the NICE scope as an outcome but vision loss was not reported as a separate outcome in the trials but is included as a complication in the economic model. The risk of vision loss is minimised by high dose GC treatment prior to baseline and by escape GC therapy throughout the trial.

The primary outcome of the GiACTA trial was, 'Proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined GC taper regimen'. To meet adherence to the protocol-defined GC taper regimen patients had to be GC free by week 26 (or week 52 according to treatment arm). Remission had to start at week 12: patients not in remission at week 12 were counted as non-responders. The CS stated in their clarification response that week 12 was chosen as the start of remission due to a requirement for a 40 week period of flare-free remission from week 12 through to week 52. The CS stated that, if met, this would provide compelling evidence of the therapeutic benefit of tocilizumab. However, in practice a patient who does not achieve remission by week 12 would not be considered a treatment failure by their physician.

3.5 Other relevant factors

The CS stated that no equality issues related to the use of EP have been identified or are foreseen.

4 Clinical Effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The ERG considers the literature searches to be generally appropriate and likely to have captured all the relevant records, but has a number of comments as follows.

Reporting

The databases used for the effectiveness review are reported as being MEDLINE and Embase (using the embase.com interface), MEDLINE in Process (using PubMED interface) to identify in-process citations and e-pubs, and CENTRAL (using the Cochrane Library). This is reported in the CS Section D1.1.1 Search Strategy.

The search strategies used in each of the 3 databases are fully reproduced in Section D.1.1.3 and the date that they were conducted is given. The numbers of records retrieved matches the number given in the PRISMA diagram provided on page 43.

Additional searches of conference websites were conducted to identify potentially relevant posters and abstracts and the reference lists of identified studies were reviewed.

Searches of the trials registers ClinicalTrials.gov and the WHO ICTRP were also conducted to find ongoing studies although nothing is reported about the search terms used or whether any studies were identified.

Strategy

The strategy used in MEDLINE and Embase consists of three sections combined with the AND search operator i.e., 1) giant cell arteritis 2) drug interventions and 3) RCT study type.

In the MEDLINE In Process search via PubMED the strategy consists of terms for 1) giant cell arteritis 2) drug interventions and 3) terms for publication status. For Cochrane, the search (correctly) consists of subject terms only.

The ERG does not have access to the embase.com interface, but notes that the overall structure of the search strategies used for MEDLINE and Embase seems to be appropriate: there are no errors in how the sets are combined; and neither are there any typographical errors in the search terms used. However, at line 8 of the Embase/MEDLINE search strategy it is not clear which fields are being searched using the 15 search terms that begin with ‘clinical trial’ and ends with ‘placebo*’. It appears that there is missing notation in these lines e.g. /de or: ab,ti

Additionally, the search of PubMED for In Process MEDLINE citations (reported in Table 2) includes 2 MeSH terms at line 1 Giant Cell Arteritis [MeSH] and line 2 [Adrenal Cortex Hormones]. These are entirely redundant as the search is trying to identify records that will not yet have MeSH indexing attached to them.

A search for grey literature is reported (at end of D.1.1.1) "Keyword-based searches using relevant disease, intervention and study design terms in Google and Google Scholar were also conducted" but no information is given about the search terms used and what was identified through these searches.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria used to select studies for inclusion in the systematic review of effectiveness of treatments for GCA are detailed in Table 4 of Appendix D.1.1.2 of the CS. The ERG considers these criteria to be appropriate. The initial criteria specified long list of interventions, but once the NICE scope was finalised so that the appraisal comparator was 'established clinical management without tocilizumab', infliximab, adalimumab, etanercept, abatacept, sirukumab, immunosuppressants, azathioprine, methotrexate, cyclosporin A and other biologics were excluded from the review. Only English language studies were to be included, but this would almost certainly screen out only secondary publications of trials of tocilizumab.

The results of the screening of the results of the literature searches are presented in Section D1.1.6 and D 1/1/7 and excluded studies with reason are listed.

The ERG does not believe any relevant trials of tocilizumab were missed.

4.1.3 Critique of data extraction

The methods of data extraction are reported in CS Section D1.1.4 and are appropriate.

4.1.4 Quality assessment

The quality assessment of the studies identified for inclusion in the systematic review of effectiveness is reported in Appendix Sections D1.1.9 and D 1.3. The assessment considered the following factors relating to quality and risk of bias:

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were groups similar at the outset of the study in terms of prognostic factors?
- Were care providers, participants, and outcome assessors blind to treatment allocation?
- Were there any unexpected imbalances in dropouts between groups?
- Did the authors measure more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis?

This assessment appeared appropriate and well conducted. Details and further commentary on the results of this assessment are given in Section 4.2.2.

4.1.5 Evidence synthesis

The CS did not present any evidence synthesis. The CS stated correctly that GiACTA was the only randomised clinical study identified in the SLR to be relevant to the decision problem, therefore a standard meta-analysis was not feasible. Furthermore, it would not be appropriate to attempt pooling of the efficacy data from the Phase III GiACTA study and the Phase II NCT01450137 study because of differences in treatment regimens and study designs.

The ERG notes that as the GiACTA trial compared tocilizumab directly with the only relevant comparator, there was no need to include an indirect comparison with other treatments.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The CS presented two RCTs of tocilizumab in GCA: the Phase II study (NCT01450137) and a Phase III RCT (GiACTA). GiACTA is the only RCT that provides data on the effectiveness of the licensed dose of tocilizumab in patients with GCA. The Phase II study (NCT01450137) provides only supporting evidence. The GiACTA trial includes both newly diagnosed and relapsing patients with GCA.

The ERG did not identify any other directly relevant trials.

4.2.1 Design of the GiACTA trial

Randomised phase (Part 1)

The GiACTA trial investigated the clinical effectiveness of tocilizumab in 251 adults over 50 years old with new-onset or relapsing giant cell arteritis. The trial was preceded by a 6 week screening phase between patients presenting with GCA flare and the trial baseline. During this pre-trial phase the flare was managed with GC, with the aim of achieving remission at baseline. At baseline patients were randomised to one of four arms, two arms of intervention treatment, which were: 162mg of tocilizumab once a week with a 26 week GC taper (TCZ QW+26) and 162mg of tocilizumab every other week with a 26-week GC taper (TCZ Q2W+26) and two arms of placebo treatment: one with a 26-week GC taper (PBO+26) and one with a 52-week GC taper (PBO+52). There were 100 patients in the TCZ QW+26 arm, 50 patients in the TCZ Q2W+26 arm, 50 patients in the PBO+26 arm and 51 patients in the PBO+52 arm.

The trial was a double-blind, randomised, multicentre, placebo-controlled study. The primary efficacy objective was the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined GC taper regimen. The secondary endpoints included the time to

GCA flare after disease remission, patient reported outcomes (PROs), and health related quality of life (HRQL). A summary of the methods of the GiACTA trial is presented in the CS Table 6 Page 29).

The ERG has the following comments about the design of the GiACTA trial. The CS is unclear about when GC tapering starts in participants. It is the ERG's understanding that patients were not all in remission at baseline (this was confirmed in the company's clarification response), but even so, all patients had to start the tapering protocol. The imposition of a tapering of the GC dose on patients not in remission and who are otherwise receiving placebo seems to be a bias against the placebo arm. This potential difference in treatment arms was not stratified for or accounted for in the analysis.

The GiACTA trial population includes both new-onset GCA (diagnosed <6 weeks before baseline visit) and relapsing GCA (diagnosed >6 weeks before baseline visit and previous treatment with ≥40 mg/day GC [or equivalent] for ≥2 consecutive weeks at any time) patients. The ERG is uncertain whether these two sets of patients would be treated similarly in clinical practice. Clinical advice to the ERG indicated that patients with new-onset GCA generally have a better outcome from GC treatment than patients with relapsing GCA: patients with relapsing GCA already have the burden of previous GC treatment with its cumulative toxicity, meaning that clinicians may be reluctant to go straight to the highest doses; and after initial response to GC, relapsing patients are then more likely to flare again during tapering, because patients who have flared once are more likely to flare again subsequently. Therefore, tocilizumab may be more beneficial in patients with relapsing GCA who have previously been exposed to GC treatment. However, new-onset patients who have experienced adverse effects from GC or are at high risk of mental health problems would benefit from tocilizumab treatment and lower cumulative doses of GC. The ERG also notes that based on a published article on the baseline characteristics of the GiACTA trial,[28] 17% of the trial patients were refractory to GC therapy, i.e. they had never achieved remission with GC.

The intervention in the GiACTA trial was 162mg of tocilizumab in combination with a tapering course of GC, which matched that specified in the NICE scope. The comparator used in the GiACTA trial was placebo in combination with a tapering course of GC. As stated in Section 2.3 the GC tapering regimens in the placebo arms are shorter than recommended practice. Only the placebo+52 week taper can be considered an appropriate comparator.

The primary outcome of the GiACTA trial was proportion of patients in sustained remission at Week 52 (following induction and adherence to the protocol-defined GC taper to reduce GC dose to zero). The primary outcome comparison was with patients receiving placebo + 26 week GC taper. The secondary comparison of the GiACTA trial was the same outcome (sustained remission at Week 52), but compared with placebo + 52 week GC taper. The ERG note that as the placebo+52 week taper is

the more relevant comparator for the present appraisal, this secondary comparison is the relevant one in terms of sustained remission.

Another secondary outcome was time to first GCA disease flare after disease remission, which is a key outcome in the economic model. Flare was determined by the investigator and defined as the recurrence of signs and symptoms of GCA and/or an erythrocyte sedimentation rate (ESR) ≥ 30mm/h attributable to GCA. Remission was defined as the absence of flare and normalisation of C-reactive protein (CRP < 1mg/dL). Patients were not at risk of flare until after remission had been achieved, however, not all patients were in remission at baseline. The CS provided the time to remission for subjects not in remission at baseline, as requested by the ERG. The median time to remission was much higher in the PBO+52 group (22 days) than the TCZ QW+26 group (8 days). This affects the follow-up time available for the time to first GCA disease flare outcome as patients in the PBO+52 group have a shorter period of time during which they are at risk of flare. Therefore, this may bias the time to first flare outcome in favour of placebo; the time to first flare is clearly longer in the tocilizumab group but this may be a conservative result due to the difference in baseline remission.

Other outcomes were annualised relapse rate, which is the number of flares between the first clinical assessment of GCA and the final clinical assessment prior to entry into Part 2, divided by the time period between; and exposure to GC, which was calculated based on a patients starting GC dose, the taper schedule (26-week or 52-week) and the assumption that a patient continued the taper without error.

Long-term follow-up (non-randomised) phase of GiACTA trial (PART 2)

Part 2 of the GiACTA trial is an open-label extension which includes patients from Part 1 who will be followed for an additional 2 years. This part of the GiACTA trial is currently ongoing; however the CS has presented some preliminary results. All patients from Part 1 were entered into the open label extension Part 2. Patients in remission at Week 52 of Part 1 are taken off tocilizumab treatment when entering Part 2 of the trial but are still followed up for maintenance of remission. Whereas, patients not in remission at Week 52 or patients who flare or relapse in Part 2 of the trial are treated with tocilizumab at the discretion of the investigator. Maintenance of remission, incidence of flare/relapse and treatment of flare is recorded during Part 2 of the trial.

4.2.2 Participant flow in the GiACTA trial

A consort diagram of the patient disposition was presented in the CS appendices (Figure 3 page 52). The ERG considers the diagram provided sufficient information on the flow of participants during the GiACTA trial.

There were 251 patients randomised in the GiACTA trial. Patients were randomised 2:1:1:1; 100 allocated to the TCZ QW+26 arm, 50 allocated to the TCZ Q2W+26 arm, 50 allocated to the PBO+26 arm and 51 allocated to the PBO + 52 arm. Overall, 41 patients were withdrawn from blinded study treatment; 18 withdrew from the TCZ QW+26 arm, 9 withdrew from the TCZ Q2W+26 arm, 9 withdrew from the PBO+26 arm and 5 withdrew from the PBO+52 arm. The most common reasons for withdrawal were adverse events (15 patients) and withdrawal of consent by the subject (10 patients). The number of patients who withdrew due to adverse events in the TCZ QW+26 and TCZ Q2W+26 arms was 9 and 3, respectively. Whereas, the number of patients who withdrew due to an adverse event in the PBO+26 and PBO+52 arms was 3 and 0, respectively. Of the 41 patients withdrawn from blinded study treatment, 34 patients discontinued Part 1 of the study: 15 patients in the TCZ QW+26 arm, 8 patients in the TCZ Q2W+26 arm, 6 patients in the PBO+26 arm and 5 patients in the PBO+52 arm. The ERG requested more information on the 8 patients who withdrew due to lack of efficacy: the trial protocol specified that following lack of efficacy of trial treatment patients were given escape therapy (GC) and retained in the trial. In their clarification response the CS stated that the majority of these 8 patients withdrew despite receiving escape GC therapy because their physician wanted to put them on alternative therapy, which was not permitted per protocol (methotrexate or IV steroids). No deaths were reported during the 52-week GiACTA trial.

There were 88 patients at the time of the Part 1 data cut (11 April 2016) who had reached the Week 100 visit of part 2 of the GiACTA trial, which is still ongoing. The duration of follow-up in Part 2 ranged from 48 to 84 weeks. In Part 2 of the GiACTA trial the number of patients in the TCZ QW+26 and TCZ Q2W+26 arms was 33 and 17, respectively. The number of patients in the PBO+26 and PBO+52 arms was 18 and 20, respectively.

4.2.3 Baseline characteristics of the GiACTA trial

The CS presented baseline characteristics for the GiACTA trial population (Table 7, Page 34 of the CS). The ERG notes that there is some lack of clarity in this presentation of the baseline details. Based on a published report of the baseline details,[28] the ERG notes that both the characteristics at diagnosis/screening and actual baseline (week 0 of the trial) need to be considered.

One important baseline characteristic missing from Table 7 is the number of patients with GC refractory GCA (who make up 17% of the total population): it is not clear if they are well balanced across the treatment groups. Another characteristic is whether the patient was in remission at baseline. The ERG queried this and in their clarification the company provided the numbers of patients in remission at baseline, by treatment group: PBO+26 arm 18 (36%); PBO+52 arm 25 (49%); TCZ QW+26 arm 44 (44%). The CS also didn't include the time since diagnosis at baseline; therefore it is unclear if this is balanced between treatment groups.

The CS stated that the baseline demographics between the treatment groups were comparable. However, the ERG believes that there were some imbalances between the two treatment groups:

- The disease duration (days) at baseline was variable across the trial arms: PBO+26 arm (364.7); PBO+52 arm (255.2); and TCZ QW+26 arm (306.8). As disease duration could be associated with difficult to treat disease, this imbalance would favour tocilizumab in comparison with PBO+26, and favour the PBO+52 arm when it is the comparator. The clinical adviser to the ERG also advised that longer disease duration may be indicative of the more difficult to treat patients.
- More patients in the PBO+52 arm had signs or symptoms of GCA (47.1%) compared to the TCZ QW+26 arm (37%). Clinical advice to the ERG indicated that, as symptoms for GCA are generally symptoms of cranial GCA (though not always), this may favour the placebo arm as it suggests there are more patients with (often easier to treat) cranial GCA in the placebo arm.
- There was a higher mean ESR in the PBO+26 arm (28.8) compared to the TCZ QW+26 arm (18.7). This may favour the TCZ QW+26 arm as it suggests that patients in the placebo arm have higher disease activity, which is not as well controlled as patients in the TCZ QW+26 arm
- A larger proportion of patients were diagnosed by temporal artery biopsy in the PBO+26 arm (72%) compared to the TCZ QW+26 arm (57%). Clinical advice to the ERG suggested that this may favour the placebo arm as it would have fewer patients with large-vessel GCA compared to the TCZ QW+26 arm.
- The ERG asked for details of vision loss at baseline in the PFC, as this was not provided in the CS. The company provided the number of patients who had a range of visual manifestations at baseline, which appear to be relatively balanced between treatment arms. The number of patients with visual impairment at baseline was very low; blurred vision was reported for 6% of patients and unilateral blindness was reported in 1 patient in each arm. Patients were treated with high-dose steroids prior to baseline, so their disease may have been less active when compared with diagnosis.

The ERG concluded that there are many baseline imbalances between the treatment groups. However, overall the differences between the arms generally balance out, with no obvious skew or leaning.

4.2.4 Summary of the quality of the included trial

The CS included a quality assessment of the GiACTA trial in accordance with the NICE-recommended checklist for RCTs (Table 9, Page 37 of the CS). The ERG considers that the trial is of relatively good quality; however there are a few issues that may increase bias (Table 1). The trial was appropriately randomised on a 2:1:1:1 ratio using an Interactive Voice Response System (IVRS) and so the number of patients in each arm was relatively even according to the ratio. Treatment allocation was concealed for the whole trial population due to randomisation being done using IVRS and

randomisation was stratified by baseline GC dose (<30mg or ≥30mg per day). Therefore, the risk of selection bias is very low.

The ERG disagrees with the CS's judgement that the two groups were similar in terms of prognostic factors. As discussed above, there were some prognostic factors which were unbalanced between the four arms in the GiACTA trial: these imbalances may slightly reduce the reliability of the study results.

The ERG confirms that the trial was double-blinded: investigators, patients and sponsor personnel were all blinded to treatment assignment. However, the GC tapering was performed in an open-label fashion up to and inclusive of the daily dose of 20 mg/day, which was then switched to double-blind for dosages below 20 mg through to 0 mg. Furthermore, patients experiencing disease flare or those who were unable to adhere to the GC tapering regimen received open-label escape prednisone therapy at a dose of at least 20 mg/day and proceeded with an investigator-defined prednisone schedule in an open-label fashion. Although, the open label use of GC may be perceived as a weakening of the trial blinding, the level of GC dosing can be considered an outcome. Furthermore, the primary outcome and many of the secondary outcomes were objective and so would not be affected by the open-label GC doses. The health related quality of life outcomes could have been affected by subjective responses of participants, increasing the risk of performance bias.

The ERG agrees that there were marginal imbalances in dropouts between treatment groups. Therefore, the risk of attrition bias is very low. Similarly, the ERG agrees that the trial did not appear to measure more outcomes than those reported. The outcomes listed in the protocol are similar to the ones reported in the CSR; however the CS only reported outcomes which were relevant for modelling cost-effectiveness. Thus, the risk for selective outcome reporting is also low. Furthermore, efficacy analyses according to the intention to treat principle were performed, with standard censoring methods used for missing data.

Statistical analysis

The analysis of the GIACTA trial can be criticised because it did not take into account the difference between new-onset and relapsing patients, nor that between those who were in remission at baseline and those who were not. Randomisation was stratified by baseline prednisone dose only. Whilst there was a significant difference in baseline prednisone dose between new-onset and relapsing patients, this stratification will not account for the other differences between the new-onset and relapsing populations.

As discussed in the publication of the GiACTA trial baseline characteristics,[28]at baseline a higher proportion of new-onset patients had their disease controlled (70.6% vs 46.2%), and a lower

proportion had signs and symptoms of GCA (32.8% vs 44.7%) and symptoms of PMR (7.6% vs 30.3%). The publications also highlights that there are important differences between new-onset and relapsing patients in baseline comorbidities, in particular higher weight and BMI in relapsing patients. However, clinical advice to the ERG notes that these differences are likely to be consequences of prior GC therapy in the relapsing group.

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

Table 1 Quality assessment and risk of bias assessment

NICE Checklist Item	CS Quality Assessment	ERG NICE Checklist QA	ERG Cochrane QA
Was randomisation carried out appropriately?	Yes	Yes	Low risk
Was the concealment of treatment adequate?	Yes	Yes	Low risk
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (baseline demographics were comparable)	No (imbalances between arms)	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes, however there were open-label GC doses above 20mg and open label GC escape therapy	Low risk for objective outcomes but high risk for subjective outcomes
Were there any unexpected imbalances in drop-outs between groups?	No	No (very marginal drop out imbalances)	Low risk
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (only those relevant to CE modelling reported in CS)	No	Low risk
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	N/A

Generalisability of the GiACTA trial to NHS clinical practice

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

- The number of patients from the UK in each arm of the trial was requested in the ERG's points for clarification. The company confirmed that there were only 15 patients from the UK who received the study drug in the GiACTA trial. Of these, 7 and 4 patients were in the TCZ-QW+26 and TCZ-Q2W+26 arms, respectively. This is a very small proportion of patients and therefore, the trial population may not be representative of the UK GCA population.

- The GiACTA trial includes both new-onset and relapsing GCA patients. Clinical advice to the ERG indicated that these two subgroups of patients would be treated differently in practice. New-onset GCA patients are typically easier to treat and can often control their disease using GC treatment within one year. Clinical advice suggested that tocilizumab would preferably be used in relapsing patients and new-onset patients who are at high risk of mental health problems, or pre-existing diabetes or osteoporosis /fragility fracture, or those who experience adverse effects from GC. Therefore, the GiACTA trial population may not be wholly generalizable to the population treated in clinical practice.
- The baseline characteristics of the GiACTA population appear to be fairly representative of the UK GCA population. However, the ERG notes that there is an important difference in the mean age of patients in the GiACTA trial (69.05 years) and that from the UK CPRD data source (73 years). The ERG considered that the age reported in the UK CPRD data source more appropriately reflects the relevant population in England and Wales. Also, overall there were a higher proportion of large vessel GCA patients than cranial GCA patients. Clinical advice to the ERG indicated that, in practice, there would typically be more cranial GCA patients. Therefore, there may be an over-representation of large-vessel GCA patients in the GiACTA trial.
- The trial uses a 26 week GC taper for three of the four treatment groups. This is much shorter than that used in UK clinical practice. Clinical advice to the ERG indicated that, in practice, the average length of GC treatment is just over 2 years. Furthermore, the tapering regimen recommended by BSR adds up to a minimum of 52 weeks.[15] Importantly, several studies have shown that both the initial GC dose and the tapering schedule appear to influence the relapse rate. Higher relapse rates have been reported in the context of clinical trials with adjuvant therapies where GC tapering is more aggressive than in routine clinical practice.[13] Consequently, although the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, uncertainty remains concerning the generalisability of this tapering regimen and the associated relapse rate to a longer GC tapering regimen (18-24 months) more conventionally achieved. In summary, the placebo arm with a 52 week GC taper is most relevant to UK clinical practice.

4.2.5 Summary of results of GiACTA

Disease Remission

The primary endpoint of sustained remission at Week 52 of both tocilizumab groups compared with patients receiving placebo + 26 week GC taper was reported on pages 38-39 of the CS. However, the placebo + 26 week taper is not a relevant comparison for UK clinical practice, as in practice a much longer taper of 52 weeks or more is used.

The NHS relevant comparison between TCZ QW+26 and PBO +52 for sustained remission at Week 52 was reported on pages 39-40 of the CS. The number of participants with sustained remission at Week 52 was significantly higher in the TCZ QW+26 arm (56.0%) compared with the PBO+52 arm (17.6%); the difference in percentage of responders was 38.35 (99% CI 17.89 to 58.81) (p<0.0001) (Table 11, Page 40 of the CS). Induction of remission had to occur within 12 weeks of randomisation to meet the sustained remission endpoint. The ERG requested the numbers and proportions of patients who were not in remission at Week 12, which was not reported in the CS. The company provided the number of patients not in remission at Week 12 and the number of patients not eligible for sustained remission, which was lower for both the tocilizumab arms compared to the placebo arms (Table 2). The patients not in remission (but eligible for sustained remission) are participants who achieved remission before 12 weeks and therefore can still meet the primary endpoint of sustained remission: the ERG calculated these numbers and present them in Table 2 for clarity. As stated earlier, the ERG has some concerns that the chance of a placebo patient, who was not in remission at baseline, achieving remission at week 12 was biased against by the imposition of the GC taper from baseline.

Table 2 Patients in remission status at Week 12 (adapted from Table 2 Company's clarification response)

Week 12, n (%)	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Not in remission at week 12	7 (14.0)	9 (17.6)	7 (7.0)	6 (12.2)
In remission at or before week 12 (eligible for sustained remission	21 (44%)	25 (49%)	83 (83%)	40 (82%)
Not eligible for sustained remission	29 (58.0)	26 (51.0)	17 (17.0)	9 (18.4)

Time to first GCA flare

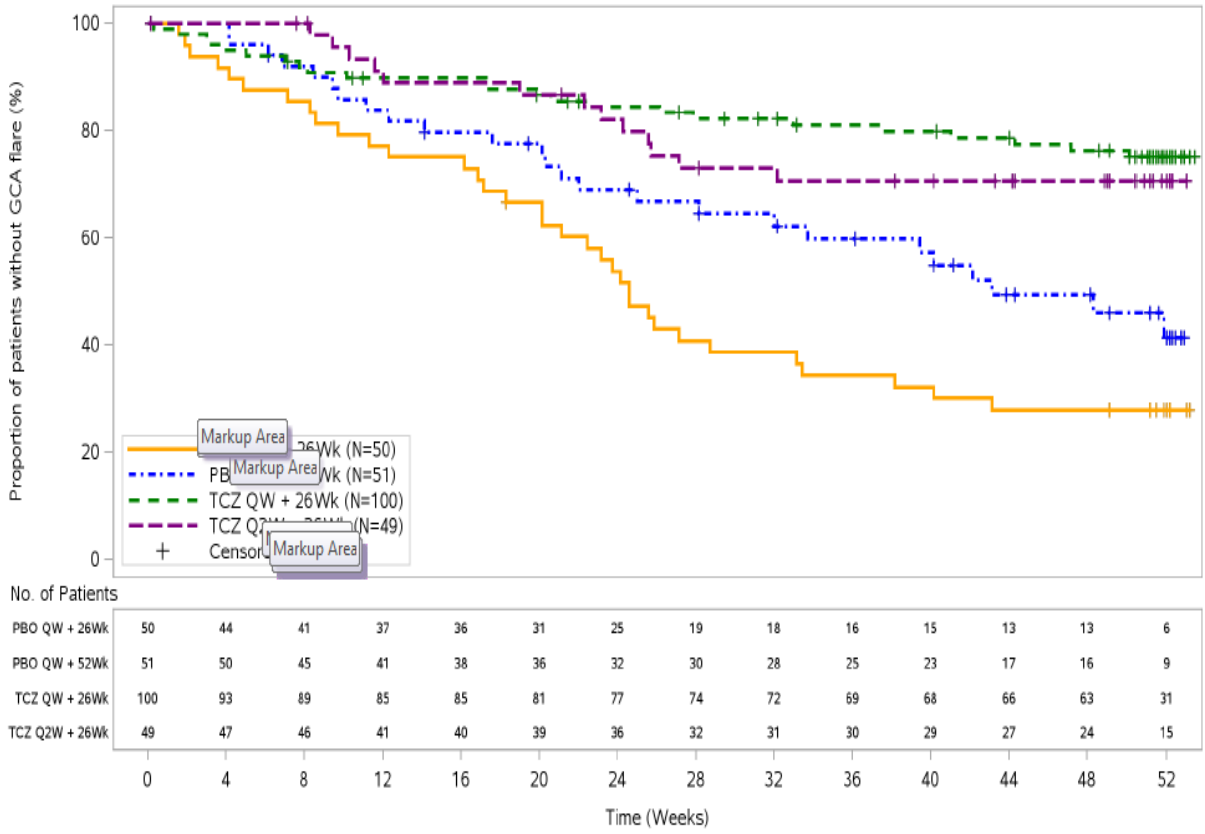
The results for time to first GCA flare are presented in Section B2.6.2 of the CS. The percentage of patients experiencing a flare by Week 52 was less for those in the TCZ-QW+26 arm (23.0%) compared to those in the PBO+52 arm (49%). Tocilizumab treatment significantly increased the time to first flare (not estimable in the TCZ QW+26 arm) compared with PBO+52 arm (295 days %% CI 168 to NE). (Analysis stratified for baseline dose of GC $\leq$ 30mg or > 30 mg/day) HR 0.39 ((%% 0.18 to 0.82) (P=0.0011).

The ERG had some queries about the time to event analysis. The CS states that patients who were never in remission were censored at Day 1. However, the KM plot presented in the CS suggests that was almost never the case. The company response clarified that only 7 patients were censored at Day 1 due to never achieving remission; 2 in each of the PBO+26, TCZ-QW+26 and TCZ-Q2W+26 groups, and 1 in the PBO+52 group. The company also clarified that 'never achieved remission' means the patient never achieved remission throughout the entire study up to Week 52. The Stone et

al. (2017) publication states that patients who never had remission were considered to have had a flare at week 0. The company clarified that the wording was in-part slightly misleading: patients who never achieved remission were censored at Week 0 (Day 1) and so were handled like a withdrawal patient rather than a flare patient. They were censored in this way for all time to flare analysis presentations. However, it may have been more appropriate to treat the 7 patients who were never in remission as flares at Day 1 rather than withdrawals.

The ERG queried the KM plot using time zero as the time when remission was achieved because not all patients who achieved remission did so before or at week 0. The CS provided the proportion of patients who were in remission at baseline (week 0): 64% in the PBO+26 arm, 51% in the PBO+52 arm, 55% in the TCZ QW+26 arm and 59% in the TCZ Q2W+26 arm. The CS also provided a table listing the time to remission for patients not in remission at baseline, by treatment group (See Appendix Table 6). The company clarified that the time to event analysis had used time zero as the time when remission was first achieved post-baseline. The time to flare is calculated as the date of flare minus the date of first remission plus one day. The CS presented an updated KM plot which also accounts for baseline remission, so that patients in remission at baseline will have a time 0 at baseline (Figure 2). The median duration of follow-up whilst at risk of flare was 167.5 days for the PBO+26 arm, 236 days for the PBO+52 arm, 358 days for the TCZ QW+26 arm and 310 days for the TCZ Q2W+26 arm. The revised curves are very similar to those provided in the original CS. The ERG analysed these updated curves as the analyses were not provided by the company. The hazard ratio decreased slightly from the previous KM analysis (HR 0.39 (99% CI 0.18 - 0.82) to HR 0.37 (95% CI 0.2-0.7), similarly showing a statistically significant lower risk of flare in patients in the tocilizumab group compared to the placebo +52 week group ($p<0.001$).

Figure 2 Kaplan-Meier plot of time to first GCA disease flare following clinical remission, by treatment group.



Annualised Relapse Rate

The mean annualised relapse rate for multiple flares observed in each patient are presented in Table 13, Page 43 of the CS. It was 1.30/year in the PBO+52 arm (median: 1) compared with 0.41/year in the TCZ QW+26 arm (median: 0). The median annualised relapse rate was 0 in the TCZ QW+26 treatment group because fewer than 50% of patients had experienced a GCA flare by Week 52.

Exposure to glucocorticoid

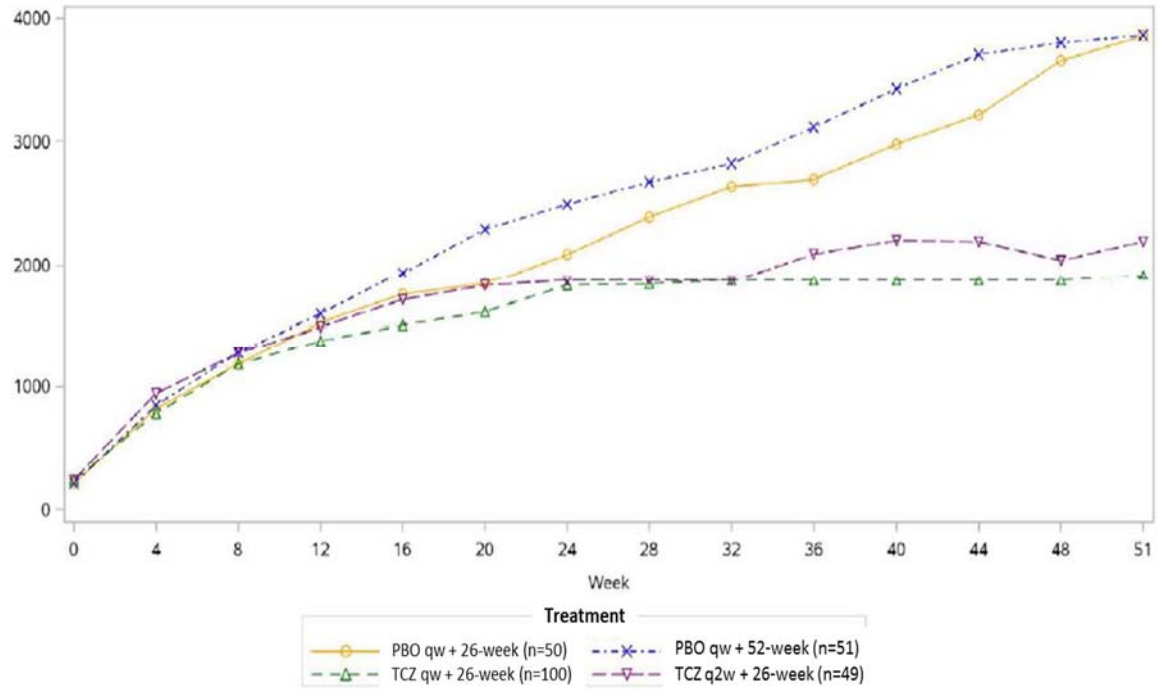
The median cumulative GC dose calculation included the open-label GC taper, blinded GC/placebo as well as escape and commercial GC (for concomitant conditions). It was presented in Table 14 on page 46 of the CS.

There was a statistically significant lower median cumulative GC dose to Week 52 in the TCZ QW+26 group (1862mg) when compared to the PBO +52 group (3817.5mg) ($p<0.0001$). The respective mean values were 2097.84 (SD 1248.45) mg and 4199 (SD 2291.32) mg. The higher cumulative GC dose in the placebo group is probably due to the longer GC taper of 52 weeks rather than 26 weeks and the increased use of escape GC therapy. There was also a notable difference in the initial GC doses taken for new-onset patients and relapsing GCA patients. In newly diagnosed patients 18% had initial GC doses of 60mg/day, whereas only 5% of relapsing patients had initial GC doses of

60mg/day. Relapsing patients who receive lower doses of GC may have a lower chance of achieving remission and thus may be more likely to discontinue GC treatment.

The CS presented a plot of the median cumulative GC dose over time (Figure 3). After Week 22, the curves for the tocilizumab treatment groups start to plateau, whereas the median cumulative GC dose continued to increase in the placebo groups. This may be due to the patients in the tocilizumab groups receiving little additional GC after their GC taper ends and escape patients in the placebo groups receiving increased steroid doses. The proportion of patients receiving GC as escape therapy were lower in the TCZ QW+26 group (23%) compared to the PBO+52 group (55%). However, the difference in median cumulative GC dose between the PBO+52 group and the TCZ QW+26 group can also be attributed to the study design of differing GC taper lengths.

Figure 3 Plot of median cumulative GC dose by visit and treatment group to Week 52 (CS Figure 4)



Health related quality of life

Health related quality of life (HRQL) was measured using four instruments: the Patients Global Assessment (PGA) of disease activity and the SF-36 (a standardised questionnaire of 36 questions) were secondary endpoints; and the FACIT-Fatigue (FACIT-F) score (a self-administered patient questionnaire that consists of 13 statements) and EQ-5D (a generic utility measure used to characterise current health states) were exploratory efficacy endpoints. Information on the completeness of the HRQL questionnaires at each time point was requested in the ERG's points for

clarification. The company provided data for all time points, which appears to be relatively balanced between treatment arms for each HRQL assessment (see Appendix Table 2).

The clinical advisor to the ERG notes that improvements in quality of life over the course of the trial are not necessarily to be expected as patients should have had their symptoms controlled by baseline, though not all were in remission. There was no notable deterioration observed in HRQL in any treatment group, however the tocilizumab groups appeared to score marginally better. Repeated measures methods were used for PGA and SF-36, so all patients were included in the analysis, regardless of their remission status. All treatment groups showed a decline (improvement) from baseline over the 52-week trial for PGA (Table 16, Page 50 of the CS). Whilst, this improvement was more pronounced in the tocilizumab treatment groups the difference between the TCZ QW + 26 group and the PBO+52 group was not statistically significant. The change from baseline to Week 52 of the SF-36 Physical Component score showed a significant improvement in the TCZ QW+26 group, compared to the PBO+52 group, which showed a slight worsening (p-0.0024, Table 17, Page 51 of the CS). Both the TCZ QW+26 group and the PBO+52 groups showed a numerical improvement from baseline in the Mental Component Score; however, there was no significant difference.

In contrast, repeated measure methods were not used for FACIT-F and EQ-5D analyses and patients were censored at flare. There was no substantial deterioration in the EQ-5D scores in any treatment group. The mean changes from baseline were relatively similar between the four groups (Table 15, Page 48 of the CS). Numerically higher mean FACIT-F changes from baseline were observed for both tocilizumab treatment groups versus the placebo groups but no statistical testing was performed. However, the FACIT-F and EQ-5D analyses only provide information on patients in sustained remission and do not reflect the HRQL differences in the entire sample.

Overall, there were only marginal differences between the TCZ QW+26 and PBO +52 groups in HRQL assessments. The only statistically significant differences was seen for and the SF-36 Physical Component Score. Therefore, there is limited evidence to indicate that HRQL improves substantially with tocilizumab compared to placebo. Furthermore, the open label GC escape therapy received by patients experiencing flare may introduce potential bias for the PGA and SF-36 HRQL outcomes; whereas these patients were censored for the FACIT-F and EQ-5D analyses.

Longer term disease control

As stated in Section 4.2.1, Part 2 of the GiACTA trial is an open-label extension which follows patients for an additional 2 years; this part of the GiACTA trial is currently ongoing, with only some preliminary results reported in the CS. Patients in remission at Week 52 of Part 1 are taken off tocilizumab, whereas, patients not in remission at Week 52 or patients who flare or relapse in Part 2 of the trial are treated with tocilizumab at the discretion of the investigator. Maintenance of remission,

incidence of flare/relapse and treatment of flare is recorded during Part 2 of the trial. Data were presented for 88 patients evaluated in Part 2 of the study. Of these, 45 had met the primary endpoint in Part 1(responders) and were therefore followed off treatment in part 2. Of the 35 tocilizumab treated responders in Part 1, 16 patients (46%) flared during Part 2. This indicates that for a sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients.

Subgroup Analyses

The CS reported that subgroup analyses had been performed for 5 pre-defined subgroups: disease onset at baseline (new-onset, relapsing), starting GC dose, previous history of remission, positive imaging with no temporal artery biopsy and no cranial symptoms at diagnosis and GCA diagnosis meeting the ACR criteria. The CS stated that the results of the subgroup analyses were consistent with the results of the overall ITT population; therefore subgroup analyses were not included in the economic model. Sub-group analyses by disease status at baseline (new-onset or relapsing) for Sustained remission at week 52, for Time to GCA flare, and cumulative GC dose were reported in the CS Appendix E.

The ERG notes that a report on the GiACTA trial by Tuckwell et al.[28] divided the trial cohort into newly diagnosed and relapsing patients. The demographic features were similar, but their baseline comorbidities suggested important differences in initial GC dose and remission status at baseline. New-onset patients had higher median starting GC doses than relapsing patients. In newly diagnosed patients 18% had initial GC doses of 60mg/day, whereas only 5% of relapsing patients had initial GC doses of 60mg/day (Table 4). A study by Labarca et al. found that GCA patients treated with an initial oral prednisone dose of >40mg/day achieved earlier prednisone discontinuation than patients treated with <40mg/day.[29] Relapsing patients who tend to receive lower doses of GC may have a lower chance of achieving remission and be more likely to discontinue GC. Therefore, tocilizumab may be more beneficial in relapsing GCA patients than in new-onset patients. Furthermore, 71% of newly diagnosed patients were in remission at baseline, whereas only 46% of relapsing patients were in remission at baseline. This highlights that new-onset and relapsing GCA patients are two subgroups that may require different treatment pathways; this issue is addressed further in Section 5.

Table 3 Median starting GC dose by disease status at baseline (new-onset/relapsing)

	Placebo QW + 52 Week GC Taper (n=51)	**Tocilizumab QW + 26 Week GC Taper (n=100)**
New-onset patients		
n	23	47
Median starting dose	35.0mg	40.0mg
Relapsing patients		
n	28	53
Median starting dose	26.8mg	25.0mg

Sustained remission at week 52 by disease status at baseline (new-onset or relapsing)

The difference in the proportion of patients achieving sustained remission at Week 52 between the TCZ QW+26 group and the PBO+52 group was similar among new-onset and relapsing GCA patients (Table 4). However, the proportion of patients in sustained remission in the PBO+52 group was lower for relapsing patients than for new-onset patients.

Table 4 Sustained remission at Week 52 by disease status at baseline (new-onset/relapsing) (adapted from CS Appendix E Table 10)

	Placebo QW + 52 Week GC Taper (n=51)	sustained remission at Week 52 **Tocilizumab QW + 26 Week GC Taper (n=100)**
New-onset Patients		
n	23	47
Sustained remission	5 (21.7%)	28 (59.6%)
Not sustained remission	18 (78.3%)	19 (40.4%)
Relapsing Patients		
n	28	53
Sustained remission	4 (14.3%)	28 (52.8%)
Not sustained remission	24 (85.7%)	25 (47.2%)

Time to GCA flare by disease status at baseline (new-onset or relapsing)

Kaplan-Meier curves of time to first flare by disease status at baseline (new-onset or relapsing) were presented in the CS Appendix E 1.3 (see Figure 4 and Figure 5 below).

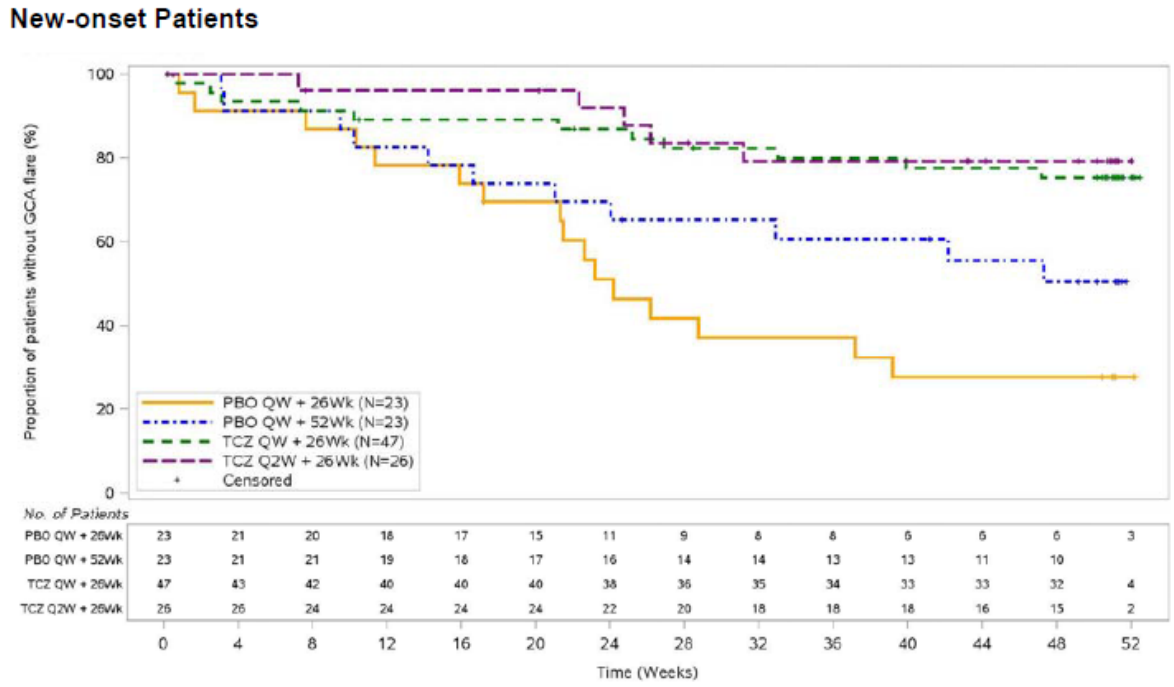


Figure 4 Kaplan-Meier Plot of Time to First Flare in New-onset patients at Baseline

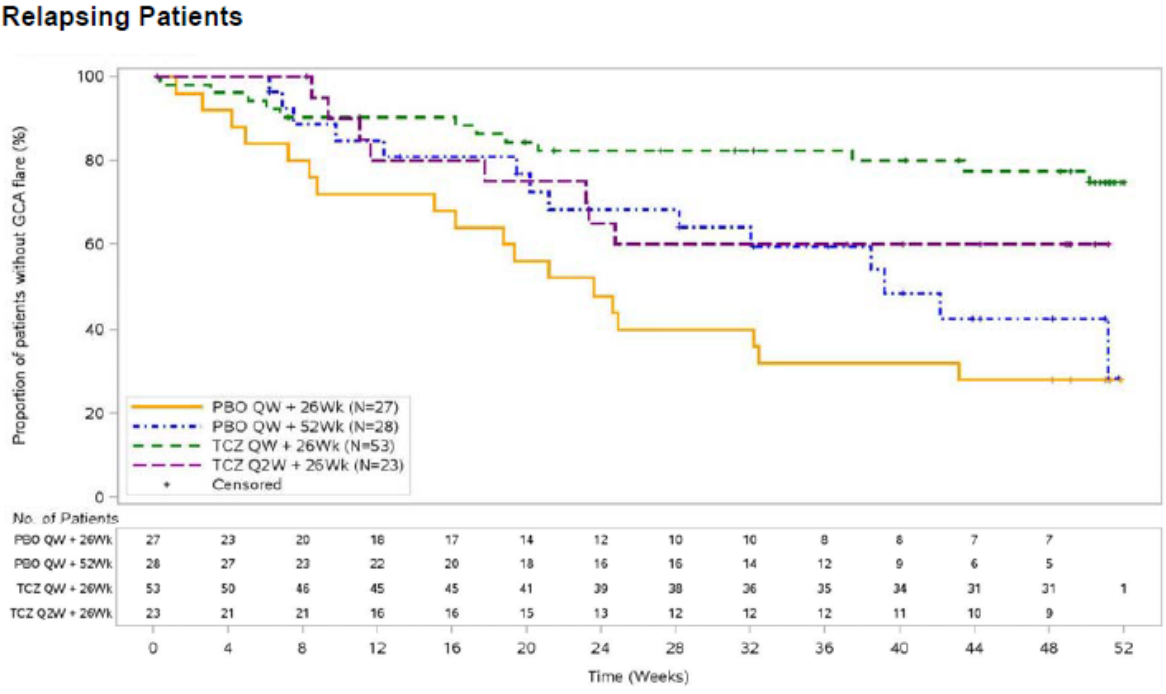


Figure 5 Kaplan-Meier Plot of Time to First GCA Disease Flare in relapsing patients at Baseline

The median time to GCA disease flare in new-onset GCA patients was 169 days in the PBO+26 group and was not calculable for the other three groups due to fewer than 50% of the new-onset patients in

these groups experiencing a flare. In relapsing patients it was 165 days in the PBO+26 group and 274 days in the PBO+52 group but was not calculable in the tocilizumab treatment groups. The CS did not report the hazard ratios for these subgroups and so the ERG performed the analysis. The median time to GCA disease flare in new-onset GCA patients was 169 days in the PBO+26 group and was not calculable for the other three groups due to fewer than 50% of the new-onset patients in these groups experiencing a flare. In relapsing patients it was 165 days in the PBO+26 group and 274 days in the PBO+52 group but was not calculable in the tocilizumab treatment groups. The ERG analysed both subgroups and found that the relative treatment effect was slightly less in the new-onset patients (HR 0.44, 95% CI 0.29 -1.59; (p=0.004)) compared with the relapsing patients (HR 0.33, 95% CI 0.14 – 0.81; (p=0.04)

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

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

Table 5 Cumulative GC dose by disease status at baseline (new-onset or relapsing) (adapted from CS Appendix E 1.4 Table 11)

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

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

4.2.6 Adverse events of tocilizumab

The CS reported on the adverse events associated with tocilizumab in GCA, which are summarised in Table 21 on page 63 of the CS. The CS presented data on common adverse events, serious adverse events (SAE) and adverse events of special interest (AESI). The total number of patients with at least one AE was similar across all treatment groups; however it was highest in the TCZ-QW group (98.0%) and lowest in the PBO+52-week group (92.2%). The proportion of patients with AEs related to GC was similar in the TCZ-QW (50.0%) and PBO+52-week group (49.0%); similarly, the number of patients with grade 3 AEs was similar in the TCZ-QW group (24%) and the PBO+52-week group (26%).

Fewer patients treated with tocilizumab experienced SAE compared with patients in the PBO+52 group; 15% in the TCZ QW+26 group and 25.5% in the PBO+52 group. None of the SAE were fatal. The proportion of patients with AE leading to withdrawal from blinded treatment was 11.0% in the TCZ QW+26 group, whereas there were no such events in the PBO+52 group. The most common system organ class (SOC) for all-grade AE and Grade 3 AE was 'Infections and Infestations', which was also an AESI based on potential safety concerns associated with tocilizumab. The CS stated there were no marked differences in the overall incidence of patients with infections between the treatment arms. However, the number of patients with 'Infections and Infestations' was notably higher in the TCZ QW+26 group (75.0%) compared with the PBO+52 group (64.7%) (Table 22, Page 64 of the CS). The number of serious infections however, was higher in the PBO+52 group (11.8%) than the TCZ QW+26 group (7.0%). The number of patients with all other AESI was relatively similar between the TCZ QW+26 and PBO+52 groups (Table 23, Page 72 of the CS).

As tocilizumab is given with the intention of being steroid sparing it might be hoped that GC-associated AEs would be lower in the TCZ QW+26 arm. In GiACTA however, the percentage of patients reporting an AE considered related to GC use by the investigator was similar in the TCZ QW+26 (50%) and PBO+52 (49%) groups. More patients in the TCZ QW+26 group had the following GC related AE: infections, general disorders and musculoskeletal and connective tissue disorders when compared to the PBO+52 group (Table 26, Page 75 of the CS). Whereas, more patients in the PBO+52 group had GC related skin and subcutaneous disorders, psychiatric disorders and eye disorders when compared to the TCZ QW+26 group.

Overall, the safety profile of tocilzumab appears to be comparable to the placebo + 52-week GC taper in the GiACTA trial, with a higher number of patients experiencing infections in the TCZ QW+26 group compared with the PBO+52 group.

4.2.7 Phase II NCT01450137 study

In addition to GiACTA a second trial of tocilizumab was identified and presented in the CS: Phase II NCT01450137 study. Details of this trial were presented in Appendix K of the CS. In brief this was a randomised, double-blind, placebo-controlled trial conducted at a single centre: the University Hospital Bern, Switzerland. Similar to GiACTA the population was people aged over 50 years with new-onset or relapsed GCA. The dose and formulation of tocilizumab studies was different to that in GiACTA (licensed). In the Phase II trial tocilizumab was delivered by intravenous infusion: 8mg/kg every 4 weeks. In both trials a tapering dose of prednisone/prednisolone was given in addition to tocilizumab.

The primary endpoint of the Phase II trial was complete remission at week 12 without clinical signs or symptoms of giant cell arteritis, and normal erythrocyte sedimentation rate and C-reactive protein at a prednisolone dose of 0.1 mg/kg per day. Relapse-free survival at week 52 was a secondary endpoint. Other secondary endpoints were time to first relapse after induction of remission, and cumulative dose of prednisolone.

Twenty patients were randomised to tocilizumab and 10 to matching placebo. The baseline characteristics are presented in Table 36. A higher proportion were newly diagnosed (77%) compared to in GiACTA (47%). Three patients discontinued tocilizumab treatment compared to five who discontinued placebo.

The CS does not make it clear what treatment patients in this trial were on immediately prior to baseline; presumably they had been treated with GC to control their symptoms (as in GiACTA). After 12 weeks, 17 (85%) patients in the tocilizumab group and four patients (40%) in the placebo group were still in complete remission, yielding a risk difference of 45% (95% CI 11–79). Adjustment for potential confounders (i.e. age, sex, baseline ESR and CRP) had no major effect on the result. At 52 weeks, 17/20 patients in the tocilizumab group and 2/20 patients in the placebo group were relapse-free. This resulted in an increase of 25 weeks (95% CI 11-39; p=0.0005) of relapse-free survival within the 52 weeks of follow-up of patients in the tocilizumab group. In addition, at Week 52 all 20 tocilizumab -treated patients were in remission, 18 of which had discontinued concomitant GC therapy.

The cumulative weight-adapted GC dose was lower in the tocilizumab patients than in the placebo arm patients, at both weeks 26 and 52: 41 mg/kg vs 66 mg/kg (p=0.0016); and 43 mg/kg vs 110 mg/kg (p=0.0005).

After week 52 tocilizumab treatment was withdrawn and patients were followed for a median time of an additional 12.5 months (range: 3–32 months). Following the last infusion of tocilizumab at Week

52, more than half of the patients (11/20) experienced GCA relapse within a median time of 5 months (range: 2–14).

Thus, the results of this Phase II trial provide supporting evidence for tocilizumab in GCA in terms of greater efficacy and GC sparing, but indicate that in many patients therapy with tocilizumab beyond 52 weeks (maybe chronic therapy) may be necessary.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic literature review and found one relevant RCT which presented clinical data on the effectiveness of tocilizumab. The GiACTA trial was a phase III, randomised, double blind, multicentre, placebo-controlled clinical trial, which was the only directly relevant trial to test the efficacy of tocilizumab. Patients were randomised in a 2:1:1:1 ratio to 162 mg of tocilizumab + 26 week GC taper (TCZ QW +26), 162mg of tocilizumab every other week + 26 week GC taper, placebo + 26 week GC taper or placebo + 52 week GC taper (PBO+52). Only the once a week dosing of tocilizumab is licensed, and therefore, this report presents tocilizumab results for this dose only. Furthermore, the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, and therefore, only the placebo+52 week taper can be considered an appropriate comparator as it is most relevant to clinical practice.

The GiACTA trial was a large, relatively good quality, double-blinded, RCT. However, there were some prognostic factors which were unbalanced between the four arms in the GiACTA trial: these imbalances may slightly reduce the reliability of the study results.

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

- The number of patients from the UK in TCZ-QW+26 the arm of the trial was only 7.
- The GiACTA trial includes both new-onset and relapsing GCA patients. Clinical advice to the ERG indicated that these two subgroups of patients would be treated differently in practice. The

analysis of the GIACTA trial can be criticised because it did not take into account the difference between new-onset and relapsing patients, nor that between those who were in remission at baseline and those who were not. Randomisation was stratified by baseline prednisone dose only. Whilst there was a significant difference in baseline prednisone dose between new-onset and relapsing patients, this stratification will not account for the other differences between the new-onset and relapsing populations. Sub-group analyses by disease status at baseline (new-onset or relapsing) for Sustained remission at week 52, for Time to GCA flare, and cumulative GC dose were reported in the CS.

- The baseline characteristics of the GiACTA population appear to be fairly representative of the UK GCA population. However, the ERG notes that there is a difference in the mean age of patients in the GiACTA trial (69.05 years) and that from the UK CPRD data source (73 years). Also, overall there was a higher ratio of large vessel GCA patients to cranial GCA patients than would be seen in NHS practice.

- The trial uses a 26 week GC taper for three of the four treatment groups. The tapering regimen recommended by BSR adds up to a minimum of 52 weeks.[15] hence, the placebo arm with a 52 week GC taper is most relevant to UK clinical practice. The 26 week taper used with tocilizumab is likely to be attempted in clinical practice, with the aim of reducing the GC load.
- Although the trial included four treatment arms the only comparison relevant to NHS practice is that between TCZ+26 and PBO+52

The number of participants with sustained remission at Week 52 was significantly higher in the TCZ QW+26 arm (56.0%) compared with the PBO+52 arm (17.6%) ($p<0.0001$). Induction of remission had to occur within 12 weeks of randomisation to meet the sustained remission endpoint. However, not all patients were in remission at baseline; 49% in the PBO+52 arm and 45% in the TCZ QW+26 arm. Therefore, the ERG has concerns that achieving remission at week 12 was biased against by the imposition of the GC taper from baseline for patients in the placebo group who were not in remission at baseline. Tocilizumab treatment significantly increased the time to first flare (not estimable in the TCZ QW+26 arm) compared with the PBO+52 arm (295 days %% CI 168 to NE) (HR 0.39 ((%% 0.18 to 0.82) (P=0.0011). Not all patients being in remission at baseline may also bias the time to first flare outcome in favour of placebo.

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

The CS reported that subgroup analyses had been performed for 5 pre-defined subgroups and stated that the results of the subgroup analyses were consistent with the results of the overall ITT population; therefore subgroup analyses were not included in the economic model. However, the ERG believes

that the subgroup analyses of new-onset and relapsing patients should have been a main result. Their baseline comorbidities suggested important differences in initial GC dose and remission status at baseline, highlighting that new-onset and relapsing GCA patients are two subgroups that may require different treatment pathways. The ERG analysed KM plots provided in the CS and found that the treatment effect of tocilizumab relative to placebo was slighter greater in relapsing patients than in new-onset patients when compared to the placebo+52 week group.

The GiACTA trial has an ongoing Part 2, which is an open-label extension including patients from Part 1 who will be followed for an additional 2 years. Preliminary results from Part 2 indicated that for a sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients. Therefore, further reliable research is needed to determine the long term effectiveness of tocilizumab in maintaining remission in patients with GCA.

The safety profile of tocilizumab appears to be comparable to the placebo + 52-week GC taper in the GiACTA trial, with a higher number of patients experiencing infections in the TCZ QW+26 group compared with the PBO+52 group.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the economic model. The critical appraisal was conducted with the aid of a checklist to assess quality and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios undertaken by the ERG to further address remaining uncertainties.

The company's economic submission included:

- A description of each systematic review conducted to identify published evidence on cost-effectiveness, HRQoL/utilities and resource usage/costs (CS, Sections B.3.1, B.3.4.1 and B.3.5.2), with further details presented in separate appendices (CS, Appendices G, H and I).

- A report on the economic evaluation conducted by the company. The report included: a description of the patient population (CS, B.3.2.1); the model structure (CS, Section B.3.2.2); the clinical parameters used in the economic model (CS, Section B.3.3); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section B.3.4), cost and healthcare resource use (CS, Section B.3.5); a summary of the inputs and assumptions used in the model (CS, Section B.3.6); the base-case deterministic cost-effectiveness results (CS, Section B.3.7.1); probabilistic and univariate sensitivity analyses (CS, Section B.3.8.1 and 3.8.2); scenario analysis (CS, Section 3.8.3); the methods of validation (CS, Section 3.10); and the final interpretation and conclusion of the economic evidence (CS, Section B.3.11).

- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply alongside additional data and analyses requested by the ERG.

- An updated Excel-based model including corrections to programming errors, alternative assumptions and additional subgroup analyses based on the ERG's points for clarification.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

The electronic databases MEDLINE, MEDLINE In-Process, EMBASE, EconLit, and the Cochrane Library's National Health Service Economic Evaluations Database (NHS EED) were searched via the OVID platform on the 8th of May 2017. The search strategies used for each database were reported in

Appendix G1.3 of the CS. The electronic searches were supplemented with an additional bibliographic review and searches of various disease-specific and HTA congresses and websites.

The structure of the search strategies for MEDLINE, EMBASE and the Cochrane Library were appropriate. Disease terms for GCA were combined with study design terms (e.g. cost-effectiveness, cost-utility) and or other relevant cost and resource utilisation terms.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria are reported in Table 13 (Appendix G1.3) of the CS. Studies of adult patients (aged 18 years and above) receiving: tocilizumab; any approved or investigational therapy; or established clinical management (including corticosteroids, aspirin and immunosuppresants) were included in the review. Articles were independently assessed by two reviewers against each eligibility criteria and uncertainty regarding the inclusion of studies was checked and judged by a third reviewer.

5.1.3 Studies included and excluded in the cost effectiveness review

A total of 314 potentially relevant articles were identified by the electronic searches and an additional two publications by the supplementary searches. 311 of these articles were subsequently excluded at the primary screening stage. The remaining 5 studies were assessed in full. Only one of these articles was included in the final review.

The single included study was based on a congress abstract and poster.[30] Orfanos *et al*. assessed the lifetime costs and consequences of two tocilizumab doses (TCZ QW and TCZ Q2W) in combination with a 26 week prednisone taper regimen compared to a 52 week prednisone taper regimen alone. The study was undertaken from a UK NHS perspective and used a semi-Markov model. The model used GiACTA trial data to estimate the impact of tocilizumab on disease control (e.g. time in remission and number of flares) and real world data from the US Market Scan Database to estimate the effect of steroid sparing. The real world data was used to quantify the relationship between cumulative prednisone dose and the risk of steroid related adverse events in GCA patients.

Although the study was formally stated to be a cost-effectiveness analysis, the study design is more appropriately defined as a cost-consequence analysis since a range of separate outcomes (or consequences) are presented and there is no attempt to combine these into a single outcome measure (e.g. LYG or QALY) .

The study reported that both doses of tocilizumab used with a 26-week prednisone tapering regimen appeared cost saving compared to a 52-week prednisone tapering regimen alone. Mean per-patient lifetime cost savings ranged between £3,255 (TCZ Q2W+26) and £3,530 (TCZ QW+26). Both tocilizumab strategies were also reported to improve GCA control (i.e. fewer relapses/flares, longer duration of sustained remission and less GCA associated adverse events) with a lower incidence of

steroid related adverse events compared to prednisolone alone. Based on these findings the authors conclude that tocilizumab is cost-effective.

The model presented by Orfanos *et al.* shares an identical structure and many common inputs and assumptions to the company model reported in the CS. The main differences between the previously published model and the company model are: (i) the company model only includes the weekly (TCZ QW+26) dose of tocilizumab based on the CHMP positive opinion; (ii) the company model uses UK specific data from the Clinical Practice Research Datalink (CPRD) to estimate the impact of a steroid sparing effect of tocilizumab; (iii) the study by Orfanos *et al.* appears to exclude the additional acquisition and monitoring costs for the tocilizumab strategies; (iv) the company model combines the separate outcomes into a single QALY measure.

A full critique of Orfanos *et al.* is not feasible given the limited details reported in the abstract and poster. However, the ERG considers that the apparent exclusion of the additional acquisition and monitoring costs from this study to be an important limitation and conclusions regarding the cost-effectiveness of tocilizumab cannot be appropriately drawn.

5.1.4 Conclusions of the cost effectiveness review

The company's search identified a single published cost-effectiveness study of TCZ QW+26 and TCZ Q2W+26 for the treatment of GCA. Given the close relationship between the previously published study and the current submission, the ERG considers that the cost-effectiveness analysis reported in the submission to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overview of the company's economic evaluation is presented in Table 6. The results of the checklist used to assess the quality of the submission are reported in Appendix table 3.

Table 6: Summary of the company's economic evaluation

	Approach	Source / Justification	Location in CS
Model	Semi-Markov model with weekly cycles. No half cycle correction was performed due to the short cycle length.	The conceptualisation of the model was stated to have been informed by the disease aetiology, trial data, NICE Scientific Advice and expert opinion (clinician and HTA).	B.3.2.2; p90-95
States and events	Seven health states: • On remission – on steroid • On remission – off steroid • On relapse/flare • On remission – on maintenance steroids • GCA-related complications	Separate remission states were used before a first flare and following the first flare to account for different transition probabilities and GC exposure based on GiACTA trial data. GCA-related complications (vision loss and stroke) were	B.3.2.; p90-95

	• Steroid-related AEs • Death	assumed to only occur from the relapse/flare state and transitions were derived from external literature. Steroid-related AEs included fractures and diabetes based on cumulative GC dose and evidence from real world data using CPRD. Death included background mortality (general population, age and gender matches) arising from any state with an adjustment for stroke related mortality attributed to GCA-related complications.	
Comparators	Tocilzumab (TCZ QW – weekly dosing over a 2-year fixed treatment duration) and prednisone (26-week tapering) Prednisone alone (52-week tapering regimen; PBO+52)	TCZ-QW was assumed to be continued over a 2 year fixed treatment period This was justified based on the CHMP Positive Opinion which states that TCZ can be continued beyond 1-year, clinical opinion and the typical duration of conventional treatment for GCA with GCs. The 52-week GC tapering regimen included in the GiACTA trial was considered a relevant comparator and was consistent the most rapid GC tapering regimen recommended in the BSR guidelines. Other immunosuppresants were not formally included as alternative strategies but some usage was assumed based on utilisation within the GiACTA trial.	B.3.2.3; p96-97
Natural History	Transition probabilities from the initial remission state to the first flare for prednisone alone (52-week tapering) were based on an individually fitted parametric model using patient-level data from the ITT population of the GiACTA trial. Transition probabilities from the subsequent remission state to flare were based on a separate Poisson regression.	An exponential distribution was assumed for the time to first flare based on statistical tests, visual inspection and external expert input. A separate Poisson regression was used to estimate the weekly probability of subsequent flare based on a post-hoc analysis of time at risk and events in the subgroup of patients experiencing an initial flare.	Section B3.3; p99-109
Treatment effectiveness	Transition probabilities from the initial remission state to the first flare for TCZ-QW (plus prednisone 26-week tapering) were based on an individually fitted parametric model using patient-level data from the ITT population of the GiACTA trial.	A weibull distribution was assumed for the time to first flare based on statistical tests, visual inspection and external expert input. A separate Poisson regression was used to estimate the weekly probability of subsequent flare based on a post-hoc analysis of	Section B.3.3.2; p100-103

	Transition probabilities from the subsequent remission state to flare were based on a separate Poisson regression.	time at risk and events in the subgroup of patients experiencing an initial flare. The effectiveness of tocilizumab was assumed to be maintained over a lifetime and justified based on early results from open label data.	
Adverse events	The risk of GCA related complications (vision loss, stroke) was derived from external literature and only applied to the flare/relapse state. The risk of GC related complications (diabetes, fracture) was based on cumulative GC dose burden and external evidence from the literature reporting the association between different levels of GC dose and the associated risk of fracture and diabetes.	The risk of GCA related complications was assumed to be related to subsequent relapse/flares. In the absence of these complications arising in the GiACTA trial, estimates were sourced from a separate published economic model comparing alternative diagnostic approaches for GCA. The use of external evidence was justified due these events being rare but associated with significant costs and HRQL implications. Cumulative GC dose for each treatment arm were based on 3 separate estimates to reflect dosing during: (i) the initial remission period (prior to first flare), (ii) during secondary remission (post-initial flare) and (iii) during relapse/flare. Dose estimates were based on data from the GiACTA trial and real world evidence.	Sections B.3.3.5. & B.3.3.6; p106-109
Mortality	Background mortality was assumed to be the same as the general population. An adjustment was made to avoid double counting the mortality attributed to stroke.	Background mortality was derived from standard lifetables and justified based on findings from a systematic review which found no significant differences in mortality for GCA patients.	Sections B.3.3.8. & B.3.3.9; p109
Health-related quality of life	Separate utilities were applied to the remission and relapse/flare states (4-weeks only). Additional utility decrements were applied to GCA and GC related complications.	Utilities for the remission and relapse/flare states were sourced from a mixed effect regression model based on EQ-5D data from GiACTA. Data was combined across the separate arms and justified given the lack of significant difference by treatment arm reported within the trial. The relapse/flare utility was applied for a 4-week duration based on published literature and clinical opinion. Utility decrements for GCA and GC-related complications were sourced from the external literature.	Section B.3.4.5; p115-117

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

5.2.1 Model structure

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

The model structure is shown in Figure 6**Error! Reference source not found.** and includes seven separate health states:

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

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

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

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

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

The four specific GCA complications and GC adverse events selected were based on a wider set of events included in a previous published model and restricted to those which were considered to have the largest impact on HRQoL and costs. The company considered this approach to be conservative as many other GC-related AEs that could be impacted by the GC-sparing effect of tocilizumab were excluded.

Figure 6: Company model structure

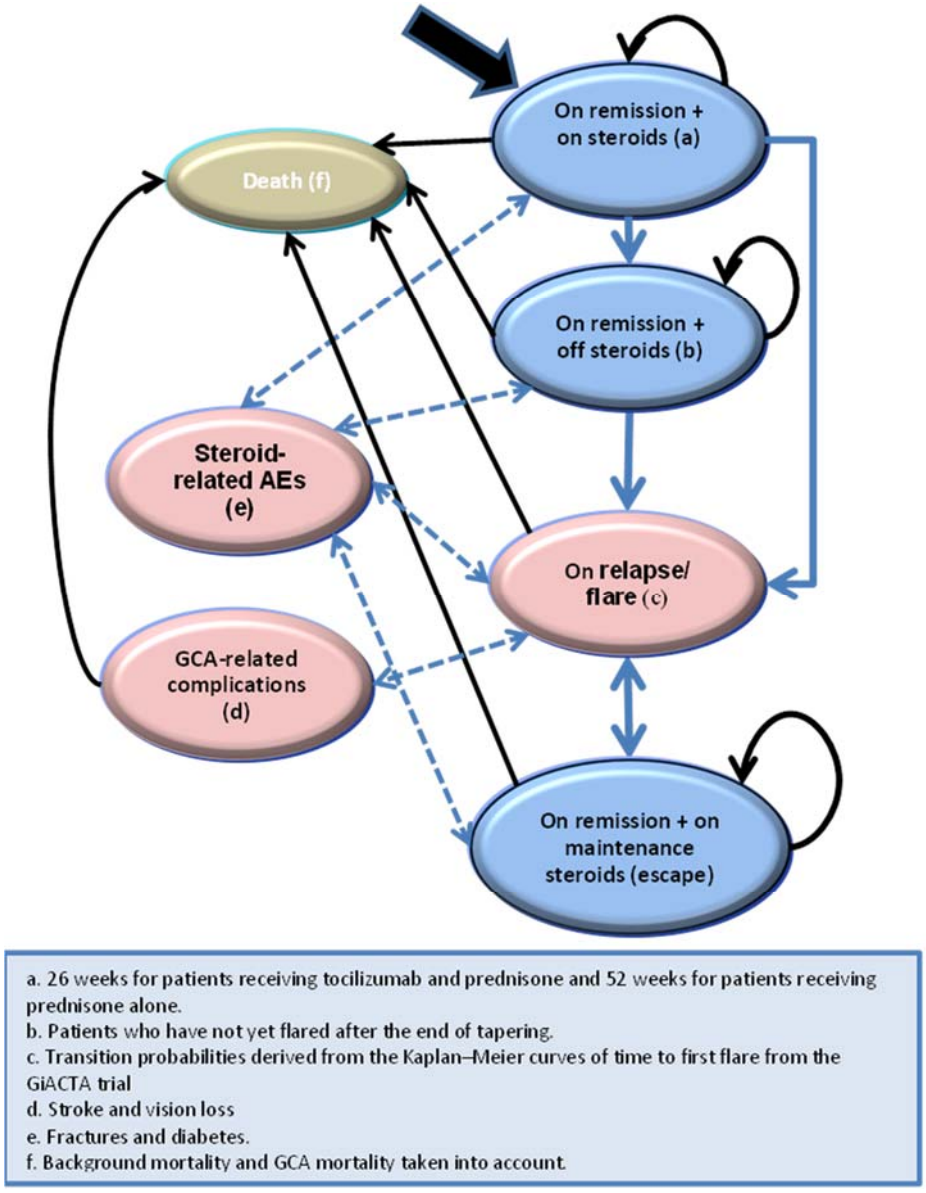


Figure replicated from company submission

The probabilities of GCA-related complications are based on a previously published model and structurally linked to the relapse/flare state. Each time a patient experiences a flare (during the initial or subsequent remission periods) they are assumed to face a risk of experiencing visual loss and/or stroke as a result of the flare. Structurally the model assumes a surrogate relationship between GCA-

related complications and relapse/flare events and that the risks of these complications are modifiable with tocilizumab treatment through a lower risk of relapse/flare.

The probabilities of GC-related AEs were derived from published real world data from CPRD reporting the association between cumulative steroid burden in GCA patients and the rate of fracture and diabetes. Structurally the model assumes that GC-related AEs can be experienced by a patient in any of the remission or flare states. However, the cumulative steroid burden calculations are not directly linked to the individual model states and so the same probability of GC-related AEs is applied to all states during each cycle.

The model assumes no excess mortality risk relative to the general population other than that arising due to one of the GCA complications (stroke). A separate death state is used to capture background (general population) mortality adjusted for stroke-related mortality. The company justified this approach based on a published systematic review which reported no overall increase in long-term mortality for GCA patients.[2]

The ERG considers that the general structure of the model is appropriate and adequately justified by the company. However, the company description of the model structure could have more clearly distinguished between events which are represented using separate and mutually exclusive health states and events which impact the state values or 'rewards' assigned to these states (i.e. cost and HRQoL implications of residing in, or transiting between, the main mutually exclusive health states). Two of the seven health states (steroid-related AEs and GCA-related complications) are not modelled as distinct health states but rather as events which impact the health state values or 'rewards' attributed to other health states and transitions. For example, GCA-related complications are included as events which impact the health state values assigned to a proportion of patients at the point they transition from a remission state to the relapse/flare state. Similarly, GC-related AEs are included as events which impact health state values for a proportion of patients within the remission and relapse/flare states.

In a similar vein, while Figure 6 depicts separate states for the initial remission period (on and off steroids), only a single remission state is actually implemented and the proportion of patients on and off steroids are used to adjust the cost and HRQoL values of the initial remission state.

The ERG's view is that the model is more appropriately described in terms of the following four main mutually exclusive health states:

- On initial remission;
- On relapse/flare;

- On subsequent remission;
- Death;

Other events such as GC-related AEs, GCA-related complications and the proportion of patients on and off steroid treatment during the initial remission period only impact the health state values attributed to these four main states.

The model uses a 1-week cycle length which is justified by the company as being in line with the dosing schedule for TCZ QW and sufficiently short that a half-cycle correction is not required. However, in determining an appropriate cycle length, the frequency of clinical events should also be considered and the cycle length should be short enough that relevant events occur at most once per cycle.[31] While a weekly cycle appears appropriate in the context of the events included in the model (i.e. multiple relapses/flares during a single week does not appear clinically reasonable), the ERG's view is that the use of a single state for the relapse/flare event may not be appropriate in the context of this short cycle length.

Structurally the model only permits patients to reside in the relapse/flare state for a single weekly cycle, whereas the associated health state values are assumed to apply over a longer duration (28 days for the duration of flare disutility and 3 months for the additional resource consequences). As a result, there appears to be an inconsistency between the structural assumptions of the model and the duration of the state values (i.e. HRQoL and costs) assigned to the relapse/flare state. This inconsistency could have been avoided by either retaining a single state for relapse/flare and employing a longer-cycle length or by creating a series of additional (tunnel) states for the flare event (e.g. relapse/flare week 1, relapse/flare week 2 etc.) and retaining the weekly cycle length.

Rather than addressing this inconsistency by structurally changing the model or altering the cycle length, the company applies a series of adjustments within the Excel model itself. These adjustments were performed by initially assigning values which captured the full duration of the HRQoL impact (28 days) and costs (3-months) of the flare/relapse event to the weekly cycle in which the event occurred and then attempting to exclude these patients from the remission state for 4 weeks in the QALY calculations to avoid double counting the same period already captured by the relapse/flare state.

The ERG identified several concerns with the nature of these adjustments as well as a significant programming error. The error was considered to have a potentially important effect on the accuracy and validity of the overall QALY estimates and the associated ICER results. These concerns are summarised below:

- The ERG considers that the adjustments introduce unnecessary programming complexities that could have been avoided by using alternative structural assumptions (e.g. alternative cycle length and/or use of tunnel states).

- An important error was also identified by the ERG in the QALY calculations. Patients who experienced a relapse/flare were only assigned the utility value associated with this state for a single week rather than the full 28-day period stated in the submission. However, these patients were subsequently excluded from the remission state for 4 weeks in the QALY calculation. This means that each time a patient experience a relapse/flare, 3 of the 4 weeks of HRQoL associated with this state are excluded. The impact of this error is likely to significantly under-estimate the QALYs attributed in the model to the relapse/flare state, creating a potential positive bias in favour of tocilizumab given the lower frequency of relapse/flare events assumed for this treatment.

- The adjustment to the QALY calculations in the subsequent remission state avoids one source of double counting. However, the inconsistencies also give rise to another potential source which is not considered. In transitioning patients to the subsequent remission state after only 1 week in the relapse/flare, these patients immediately face the risk of a further relapse/flare. That is, although the duration of a relapse/flare episode is assumed to impact on HRQoL for 4 weeks, the model structure means that patients are at risk of repeat relapse/flare events after 1-week of their event. The ERG was doubtful regarding the clinical plausibility of this.

- Although an adjustment was made to avoid double counting within the QALY calculations, a similar adjustment does not appear to have been undertaken in terms of costs. Hence, patients who experience a relapse/flare appear to be assigned the full 3-month cost during the weekly cycle in which they reside in the relapse/flare state. However, in the following cycle these patients then transition to the subsequent remission state and continue to accrue the weekly costs of this state without any adjustment for the period of time already accounted for by assigning the full 3-month cost estimate following a relapse/flare. Hence, these patients are then assigned an additional 11 weeks of cost in the remission state. This appears to significantly over-estimate the costs attributed in the model as a result of relapse/flare and creates a potential positive bias in favour of tocilizumab given the lower frequency of relapse/flare events.

These concerns were raised with the company as part of the clarification stage and revisions were requested. In their response, the company acknowledged the errors identified by the ERG in the QALY calculations and provided a corrected and updated model and a complete set of revised results. The ERG was satisfied with the corrections but retains the view that a monthly cycle length or tunnel states would have been more appropriate. These structural changes would also have avoided the issue

that patients face the risk of a further relapse/flare after 1 week. However, the ERG does not believe that this issue creates a significant bias and considers the approach sufficient for decision-making purposes.

The company's response also addressed the concerns regarding the lack of a similar adjustment applied to the cost calculations. The company clarified that the costs assigned to the flare/relapse state were considered to represent additional costs that would be incurred on top of the background management costs applied to the remission states. The ERG considers that the implementation in the Excel model is consistent with the company's response. However, the ERG notes that uncertainty remains regarding whether it is appropriate to include these background costs in addition to the 3-month event cost assigned to the relapse/flare state.

The submission states that patients enter the model either on relapse/flare or in the remission (and on steroid) state. However, all patients in the Excel model actually start in the remission (and on steroid) state. The initial transitions (i.e. remaining in remission or experiencing a first relapse/flare event) are informed from the Kaplan-Meier data (ITT population) reported in the GiACTA trial on the time to first flare after clinical remission of GCA. The reason for the apparent discrepancy between the wording of the submission and the implementation in the Excel model is not explained in the submission.

The use of the Kaplan-Meier data within the model raises several issues. Firstly, not all patients in the GiACTA trial had achieved clinical remission at the start of the study and secondly several of these patients never achieved remission during the course of the follow-up. The second issue appears to be captured within the time to first flare Kaplan-Meier data as these patients are treated as an event which occurs at day 1. However, for those patients who were not in remission at the baseline assessment but then subsequently achieved remission, the time period prior to this remission does not inform the Kaplan-Meier data or the model inputs.

These issues were also discussed in the clinical effectiveness review and further clarification and additional Kaplan-Meier data were provided by the company (See Section 4.2.5). The ERG notes that the additional Kaplan-Meier data was not incorporated in the revised model. However, although the period prior to remission is not formally captured in the model, the ERG does not consider that this leads to any significant bias as the evidence does not suggest that this period is longer with tocilizumab and that the approach used may be argued to be conservative.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 7 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case.

Table 7: NICE reference case and commentary

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	The NICE scope defined the comparator as 'established clinical management'.	Partially	The comparator included in the model was based on the 52-week tapering GC regimen in the GiACTA trial. Although the 52-week tapering period is consistent with the most rapid taper regimen advocated by the BSR/BHPR guidelines, clinicans typically will use a longer tapering regimen in routine clinical practice (18-24 months). Hence, there exists some uncertainty regarding the generalisability of the results from the 52-week tapering regimen to conventional NHS practice. The company's economic evaluation is based on the same GC regimen (prednisone) used within the GiACTA trial. However, prednisolone is more commonly used within the NHS and has a lower acquisition cost than prednisone.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective - costs	NHS and PSS	Yes	
Perspective - benefits	All health effects on individuals	Yes	
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	The economic model is stated to be a lifetime. This is assumed to be 30 years which appears reasonable based on the average age at baseline (69.05 years) and the potential lifelong consequences of complications and adverse events.
Synthesis of evidence on outcomes	Systematic review	Yes	
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Utilities for the remission and relapse/flare states were sourced from a mixed effect regression model based on EQ-5D data from GiACTA. Utility decrements for GCA and GC-related complications were sourced from the external literature.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	
Source of preference data	Representative sample of the public	Yes	
Discount rate	3.5% on costs and health benefits	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was conducted as well as deterministic sensitivity analyses. Mean increment results for the probabilistic sensitivity analysis were presented as well as graphical results using scatter plots, cost-effectiveness acceptability curves and tornado diagrams.

5.2.3 Population

The economic model was based on the overall ITT population in the GiACTA trial. Separate analyses were not provided in the initial company submission for the two main patient subgroups identified within the NICE scope (newly diagnosed and relapsed/refractory). The company justified their focus on the overall ITT population based on the favourable cost-effectiveness results for the overall population, the lack of difference in efficacy reported between the subgroups and the low statistical power.

The ERG considers the exclusion of these patient subgroups to be an important omission. These subgroup analyses were pre-specified within the statistical analysis plan and none of the reasons stated by the company appear sufficient to preclude these analyses being presented alongside those based on the overall ITT population. Indeed, it is possible that variability (i.e. differences that appear to occur between patients by chance) in the GiACTA trial results may actually be explained by observable differences in patient characteristics. The newly diagnosed and relapsed/refractory populations represent potentially important indicators of heterogeneity (i.e. difference that occur between patients that can be explained) which warrants further investigation.

Although the company reported a lack of difference in efficacy between these subgroups, the clinical and statistical basis for this conclusion is unclear. The ERG also notes that a lack of a clinically meaningful difference in efficacy between the subgroups would be evident if the cost-effectiveness results for each subgroup were similar to the results overall ITT population. However, in the absence of any cost-effectiveness results reported by the company for these subgroups, it was not possible to confirm the company's statement and/or to demonstrate that any difference which does exist across the subgroups does not lead to meaningful differences in the cost-effectiveness results.

The ERG requested analyses and results for the following subgroups: (i) newly diagnosed GCA and (ii) relapsed/refractory GCA. These additional analyses were subsequently provided by the company in response to the points for clarification. Section 5.2.10 reports the additional cost-effectiveness results provided by the company for these subgroups.

5.2.4 Interventions and comparators

The cost-effectiveness analysis was based on a comparison of two of the four treatment arms from the GiACTA trial: TCZ-QW + 26-week prednisone taper and placebo-QW + 52-week prednisone taper. The TCZ-QW dosing regimen was selected in line with the CHMP positive opinion for marketing authorisation. Although prednisone is not licensed for GCA, glucocorticoids are the mainstay of treatment for patients with GCA. The company also stated that the comparator treatment and dosing schedule is consistent with the most rapid taper regimen recommended by existing BSR/BHPR

guidelines. The company did not formally include other steroid-sparing treatments as separate comparators but noted that their use was permitted within the GiACTA trial at a stable dose.

The comparator regimen included in the model was considered by the company to appropriately reflect the final NICE scope, which simply stated that the comparator should be established treatments. The submission noted that while the 52-week prednisone tapering regimen was consistent with the most rapid taper regimen, clinicians often use a longer tapering regimen in routine clinical practice (typically 18-24 months). The submission also highlighted that a longer tapering regimen could lead to a greater cumulative steroid burden in clinical practice compared to that observed in the GiACTA trial. However, the sub mission did not discuss other issues that might affect the generalisability of the GiACTA trials results to routine clinical practice. Importantly, several studies have shown that both the initial GC dose and the tapering schedule appear to influence the relapse rate. Higher relapse rates have been reported in the context of clinical trials with adjuvant therapies where GC tapering is more aggressive than in routine clinical practice.[13] Consequently, although the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, uncertainty remains concerning the generalisability of this tapering regimen and the associated relapse rate to a longer GC tapering regimen (18-24 months) more conventionally used.

Clinical advice received by the ERG indicated that patients in England and Wales would be likely to be treated with prednisolone rather than prednisone. This is supported from UK data from CPRD which reported that 99.7% of GCA patients received prednisolone.[7] The current list price of prednisolone (5mg, 28 tablets = £0.81) is lower than prednisone (5mg, 30 tablets = £26.70). The ERG therefore requested further justification for assuming the cost of oral prednisone rather than prednisolone and an additional scenario assuming the lower acquisition cost of prednisolone. In their response, the company agreed that prednisolone is recommended in current guidelines and altered their costing assumptions accordingly as part of their revised model and base-case analyses. The results presented in Section 5.2.10 are based on these revised analyses.

The intervention being assessed is TCZ-QW combined with a much shorter prednisone tapering regimen (26 weeks) than routinely used in clinical practice. There exists some uncertainty whether in routine practice clinicians will follow the more rapid steroid tapering regimen alongside tocilizumab. However, clinical advice received by the ERG supported the view that clinicians would seek to taper steroids more quickly with adjuvant use of tocilizumab.

There also exist important uncertainties regarding the appropriate duration of treatment with tocilizumab. Although the GiACTA trial assessed 52-week continued treatment with TCZ-QW, the CHMP Positive Opinion for Marketing Authorisation states that TCZ-QW can be given beyond 52

weeks depending on disease activity, physician discretion, and patient choice. The company base-case analysis assumes that TCZ-QW will be used continuously for a 24-month period. The duration of treatment was justified as being consistent with the current duration of conventional steroid treatment, where clinical practice aims to withdraw therapy as early as possible without risking a GCA relapse/flare. However, in the absence of a clear stopping rule for tocilizumab there remains significant uncertainty concerning the appropriate duration of tocilizumab treatment.

The uncertainty surrounding the optimal duration of tocilizumab treatment has important implications for the cost-effectiveness results. The cost-effectiveness of continued use of tocilizumab beyond the 52-week period reported in the GiACTA trial will be significantly influenced by the uncertainty and assumptions made concerning the ongoing efficacy of TCZ-QW over longer treatment durations.

A key assumption applied in the base-case analysis is that the efficacy of tocilizumab over longer treatment durations will follow the same trend as observed in the within-trial period. Although the company presented scenario analysis for alternative fixed durations of tocilizumab treatment (between 12 and 60 months), these scenarios only address one aspect of the uncertainty; the cost implications of alternative treatment durations. As such, these scenarios only partially represent the extent of uncertainty in the cost-effectiveness results since identical efficacy is assumed across each scenario.

This uncertainty and implications for the cost-effectiveness results are further explored by the ERG in Section 6.

5.2.5 Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS). The time horizon used in the model was 30 years, assumed to be equivalent to a lifetime horizon. The use of a lifetime horizon is appropriate since several GCA-related complications and GC-related adverse events have lifetime HRQoL and cost consequences. However the ERG considers that there are significant uncertainties relating to the extrapolation assumptions employed within the economic model that have not been fully addressed in the company submission.

5.2.6 Treatment effectiveness and extrapolation

The effectiveness of TCZ-QW+26 versus prednisone alone was assessed in terms of the impact on GCA control (time in remission, number of flares and GCA related complications) and the impact of steroid sparing (cumulative prednisone dose, GC related adverse events). Effectiveness data was derived from the GiACTA trial (time in remission, number of flares), external literature (GCA related complications) and real world data (GC related adverse events).

The main health state transitions, assumptions and sources are summarised in Table 8 and are described in more detail in the following sections.

Table 8: Main health state transitions

Transition	Assumption	Source
Remission to relapse/flare	Time dependent, calculated from GiACTA trial data of the time to first flare event and extrapolated over a lifetime using separate parametric survival distributions fitted to individual treatment arms.	GiACTA trial data (secondary endpoint, ITT population)
Remission (escape) to subsequent relapse/flare	Constant, calculated from GiACTA trial data based on the time at risk and number of subsequent events following a first flare event. Extrapolated over a lifetime using poisson regression.	GiACTA trial data (post-hoc subgroup analysis)
GCA-related complications from relapse/flare (vision loss and stroke)	Derived from external literature and applied to each relapse/flare event.	Luqmani et al, 2016
GC-related AEs from all states receiving GC (fractures and diabetes)	Derived from real world evidence using CPRD study to estimate the risk of AEs based on cumulative steroid dose.	Real world CPRD data
Death from any state	Mortality risk based on general population mortality with an adjustment for stroke mortality.	National statistics

Table adapted from company submission

Transition – Remission to relapse/flare

Transitions from the initial remission states (on steroid and off steroid) are estimated via time-dependent transition probabilities. These are based on separate parametric survival models fitted independently to each treatment arm using patient-level data from the ITT population of the GiACTA trial.

The use of independently fitted parametric models was justified by the company based on a visual assessment of the log-cumulative hazard plots. The plots support the use of individually fitted survival models, rather than covariate based approaches using proportional hazards (PH) or accelerated-failure time (AFT) models. Alternative parametric models were then fitted to each individual treatment arm and distributions were selected based on visual inspection and formal statistical tests using the Akaike Information Criterion (AIC).

The best fitting distributions for the ITT population with the lowest AIC were the Weibull distribution for TCZ-QW+26 and the exponential distribution for the 52-week prednisone taper regimen alone. The results of the chosen parametric models were stated to have been validated based on clinical opinion and market research.

Figure 7 illustrates the Kaplan-Meier curves for each treatment arm based on the ITT population and the resulting extrapolations based on the alternative parametric functions assigned to each treatment arm.

Figure 7: Parametric extrapolation of time to first flare and Kaplan-Meier curves (ITT population)

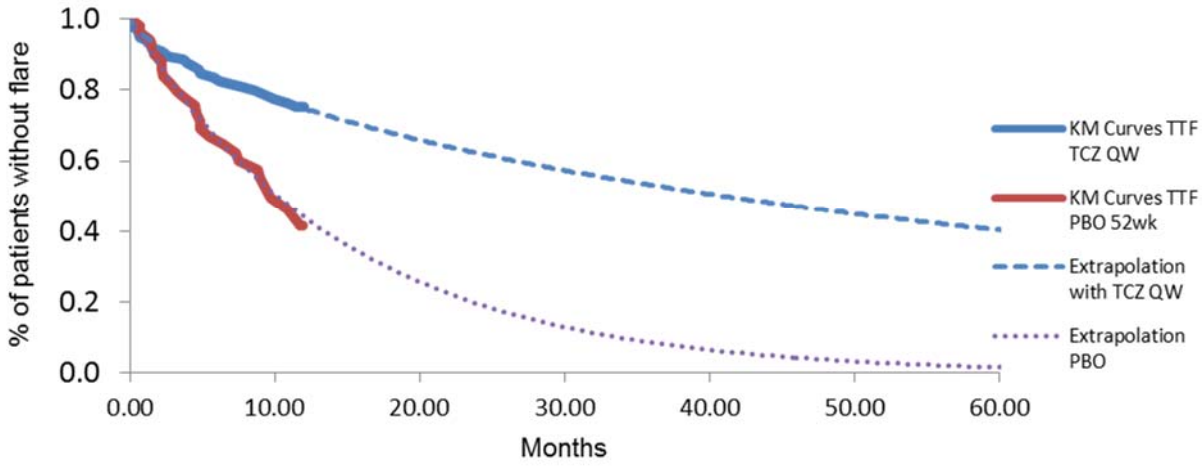


Figure replicated from CS

Figure 8 shows the longer-term predictions from the parametric function, clearly illustrating important additional gains (i.e. the area between the individual curves) are assumed beyond the discontinuation period.

Figure 8: Longer-term parametric extrapolation of time to first flare (ITT population)

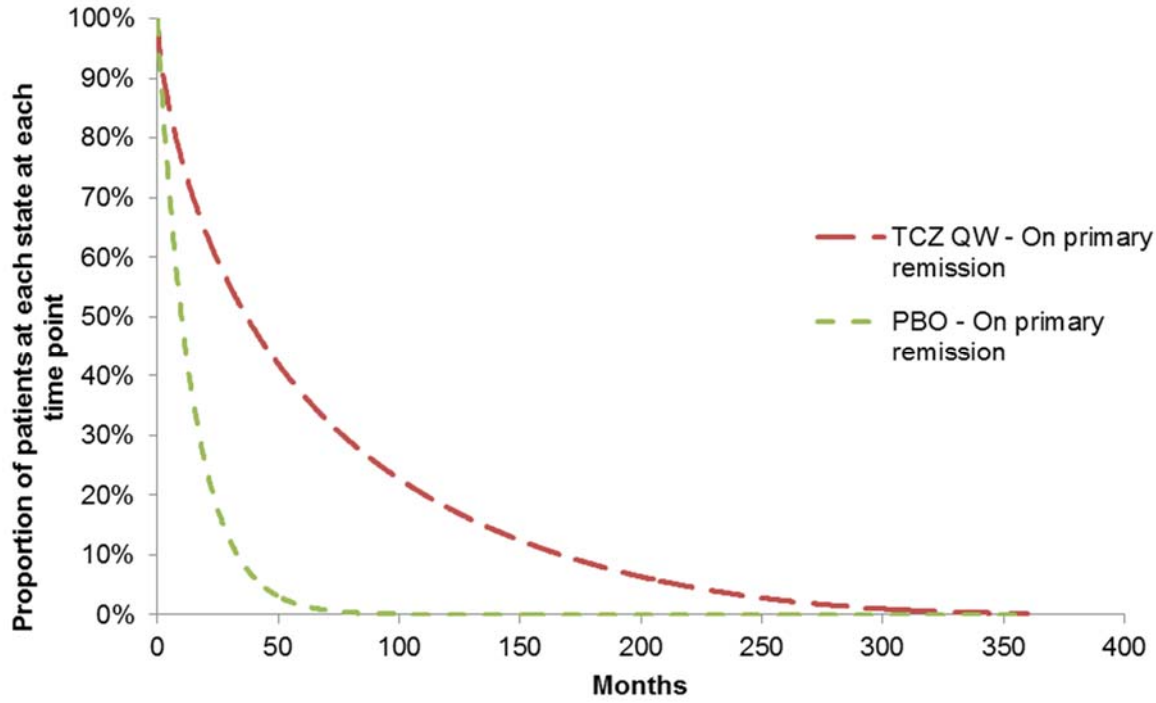


Figure replicated from CS

While fitting separate parametric models to individual treatment arms appears justifiable, it is important to note that fitting different *types* of parametric model (for example a Weibull for one treatment arm and an exponential for the other) to the separate treatment arms requires additional justification, as different models allow very different shaped distributions. Current guidance from the NICE Decision Support Unit (DSU) state that in circumstances where the proportional hazards assumption does not seem appropriate, the most sensible approach is to fit separate parametric models using the same parametric distribution allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution.[32]

The ERG notes that no additional justification was provided by the company for using different types of parametric model. While the different types of distributions provides the best statistical fit to the observed data (i.e. high internal validity), the AIC tests did not indicate large differences in goodness of fit across the distributions. Furthermore, these tests do not address the external validity of the resulting extrapolations.

Table 9 summarises the goodness of fit statistics (AIC values) for each parametric distribution. The best fitting (lowest AIC) distributions for each population are highlighted by the ERG in bold: ITT population – TCZ QW+26 (Weibull), PBO+52 (Exponential); Newly diagnosed subgroup - TCZ QW+26 (Exponential), PBO+52 (Exponential) and Relapsed/refractory subgroup - TCZ QW+26 (Exponential), PBO+52 (Lognormal).

Table 9: Summary of goodness of fit statistics for time to first flare (TTFF)

	ITT population		Newly Diagnosed		Relapsed/Refractory	
	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper	TTFF in TCZ QW + 26-wk GC taper	TTFF in PBO QW + 52-week GC taper
EXPONENTIAL	176.33073	**118.04365**	**85.42530**	**59.11030**	**92.89860**	60.57836
WEIBULL	**174.88006**	119.03899	85.68266	61.10613	93.19271	60.20129
LNORMAL	175.02922	118.10141	85.73792	60.33805	93.28869	**59.88400**
GAMMA	176.82294	118.10068	87.66579	62.20861	95.15233	62.08643
LLOGISTIC	174.90303	118.81808	85.71293	60.79097	93.18509	60.46400

Table replicated from company response, Table 20 p51

For each subgroup, the same parametric distributions used for the ITT population (Weibull and exponential) was applied and justified by the company based on consistency. However, while the best fitting distributions were used for the ITT population, there were alternative distributions with better statistical fits for each of the subgroups. Again, the small differences in AIC statistics do not indicate important differences in fit based on the trial period.

In circumstances where survival data require substantial extrapolation it is important to attempt to validate the predictions made by the fitted models by other means. The submission stated that the extrapolations for the ITT population were validated by comparing the proportion of patients on sustained remission to the expert clinical opinion and market research. The extrapolations were reported to be externally valid as the model output was consistent with estimates from these external sources.

The ERG identified several concerns regarding the approach and assumptions used by the company to inform the transition probabilities from the initial remission state to relapse/flare:

1) The references to expert clinical opinion and market research in the CS were unclear in relation to the associated statements of external validity. The selected parametric distribution (exponential) for the 52-week prednisone taper predicts that less than 2% of patients will not have experienced a first relapse/flare by 5 years. However, several longitudinal cohort studies of GCA patients with long term follow-up data report a significantly higher proportion of patients receiving GC that have not experienced a flare by 5 years (approximate range 30-50% across these studies).[13, 17, 29, 33] Furthermore, these studies also appear to suggest that the hazard of relapse/recurrence tends to decrease during long-term follow-up, suggesting reduced disease activity over time.[34]
2) The future trajectory of patients in the GC alone arm beyond 52-weeks is likely to follow a different trend than the period up to 52-weeks. The period up to 52-week covers the duration of the tapering period during which time patients are at highest risk of a relapse/flare event. Although patients who are successfully tapered will still face a risk of a future relapse/flare event,

inevitably these risks are likely to follow a different longer term trend than that observed during the tapering phase.

3) The assumption that patients who continue to receive TCZ beyond 52-weeks will follow a similar future trajectory as experienced during the observed follow-up period is clearly uncertain. While the Weibull distribution appears the best fitting distribution to the observed data, uncertainty exists regarding the use of this function over longer treatment durations.
4) A key assumption made in the base-case analysis is that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration period. Within the economic model this is implemented by maintaining patients on the separate parametric survival function over the entire model horizon (i.e Weibull and expontential). Hence, both treatment specific and different types of parametric functions continue to be assumed over the entire extrapolation period. Consequently there is no attempt to structurally link the treatment duration period for tocilizumab to the parametric survival modelling approach. The structural disconnect means that the scenarios presented by the company concerning alternative treatment duration only consider the impact of differences in treatment costs.

This assumption that the benefits of tocilizumab treatment continue over a lifetime is justified in Table 31 of the submission on the basis that "*early results from the OLE (open label extension study) suggest that very few patients re-flare after treatment with tocilizumab*". However, Table 48 of the submission (and data reported in section B2.6.6) also state that "*50% of patients relapsed/flared after withdrawing tocilizumab therapy*". This figure appears similar to that reported by Adler et al (2016) following cessation of tocilizumab in the previous RCT, where the authors concluded that "*clinical and serologic remission in response to TCZ (tocilizumab) for 52 weeks does not result in relapse-free survival after termination of treatment*".[35]

The ERG is concerned that the assumption that the benefits of TCZ continue over a lifetime regardless of the treatment duration does not appear justifiable based on early results from the OLE study and the published results from the previous RCT. The external evidence identified by the ERG also raises uncertainties regarding the external validity of the extrapolated results for the prednisone 52-week taper.

The ERG requested further justification and evidence from the company to support the selected parametric distributions and the external validity of the longer term predictions. The company response stated that:

"*there is substantial variability between clinical opinions sought by Roche and published articles regarding the rate of flare/relapse and the time a GCA patient is at risk of these. This variability*

meant that we were unable to unanimously validate or dismiss some assumptions, nor we were able to find a suitable alternative" (Clarification response, p24) .

The ERG also requested additional justification to support the appropriateness and validity of the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration and clarification. As part of the company's clarification response, they noted a number of limitations of the OLE data regarding the robustness, design and limited precision due to small numbers. The company also stated that

"*Roche recognise the duration of treatment benefit attributed to tocilizumab in the treatment of GCA patients is highly uncertain and highly impactful on the cost-effectiveness estimate. We have attempted to engage clinical opinion on this area of uncertainty, both during the dossier development and again in response to these clarification questions. However, clinical opinion varied, and clinicians were also highly uncertainty on this point*" (Clarification response, p25).

The ERG does not consider that these uncertainties have been fully addressed in the company submission or their response. These uncertainties are further explored by the ERG in Section 6.

Transition – Remission (escape) to subsequent relapse/flare

Transitions from the remission (escape) state to subsequent relapse/flare are based on constant transition probabilities. These probabilities are estimated using a Poisson regression based on a post-hoc analysis of the subgroup of patients experiencing an initial flare. The Poisson regression uses data from the time of the first flare until the end of the follow up and the observed number of subsequent flares during this period. An annualised relapse rate is estimated based on the number of flares during this period, divided by the time period (in days) and then multiplied by 365.25. These rates are then converted to weekly transition probabilities in line with the weekly model cycle.

Table 10 summarises the weekly probabilities for the ITT population and for the subgroups requested by the ERG.

Table 10: Summary of transition probabilities - Remission to relapse/flare

Population	Treatment arm	Mean rate (in log scale)	Standard Error	Mean days follow-up used within the analysis	Weekly probability of flare
ITT	Tocilizumab QW	-1.056	0.354	228	0.0106
	Placebo 52 week	-0.300	0.224	224	0.0228
Newly Diagnosed	Tocilizumab QW	-0.875	0.447	228	0.0127
	Placebo 52 week	-0.619	0.378	224	0.0166
Relapsed/ Refractory	Tocilizumab QW	-1.299	0.577	228	0.0083
	Placebo 52 week	-0.074	0.277	224	0.0285

Table replicated from company response (Table 21, p54)

In general, the results presented in Table 5 appear clinically logical in terms of the natural history. That is, the risks of subsequent flare for PBO+52 appear higher in the relapsed/refractory than the ITT and Newly Diagnosed populations. However, the ERG notes that that subgroup results report a lower absolute risk for TCZ QW+26 in the relapsed/refractory subgroup (weekly probability = 0.0083) than the equivalent risk in the newly diagnosed subgroup (0.0.127), suggesting a larger relative treatment effect in this subgroup. Although the ERG considered that a subgroup specific effect was clinically plausible, the finding that the absolute risks were lower in the tocilizumab arm of this subgroup was considered less plausible. This suggests that using subgroup specific relative effects for this transition within the model may not be appropriate. This issue is further in Section 6 by the ERG.

The CS also assumes that these transition probabilities are constant over time, suggesting that patients remain at ongoing risk of further flares for the remainder of their lifetime. A single reference was provided to support this assumption, with the company noting that flares can occur many years after initial diagnosis. The company also presented additional scenario analyses where the transition probabilities were reduced over time (5% and 10% annual reduction) recognising that many patients do not require continuous treatment.

The ERG identified further concerns regarding the approach and assumptions used by the company to inform the transition probabilities from the remission (escape) state to subsequent relapse/flare:

1. The evidence used to inform this transition is based on a post-randomisation subset of the ITT trial population. This means that the evidence used does not constitute a randomised comparison, and will be subject to confounding by both observed and unobserved covariates. This introduces

additional uncertainty and potential bias within the effectiveness estimates applied to this transition.

2. The use of a post-randomised subset also introduces an important source of selection bias. That is, the subgroup of patients who experienced a flare during the follow-up of the GiACTA trial is unlikely to representative of the entire ITT population. The prognosis of patients who relapse/flare early in the course of their treatment is likely to be different from patients who relapse/flare later. This is important because patients who did not experience a relapse/flare during the GiACTA trial follow-up period do not contribute any data to inform the transition from the remission (escape) state to subsequent relapse/flare. However, since all patients receiving prednisone alone are assumed to relapse/flare at some point during the period of extrapolation, ultimately the longer-term prognosis of all patients in the model will at some point will be informed from data entirely based on the post-randomised subset.
3. Within the CSR additional data is provided on the remission and flare status for each individual patient at each follow up assessment. The ERG reviewed these individual records and noted that there were several patients who were reported to be in 'flare at visit' during consecutive follow-up times (e.g. at weeks 44 and 48). The ERG was uncertain whether these were being treated as separate flare events or a single event within in the Poisson regression. The ERG was concerned that treating these as separate flare events might over-estimate the risk of a subsequent flare/relapse.
4. The total mean number of flares (19.67) predicted by the model over a 30-year period for the ITT population appears high for the prednisone alone comparator based on longer-term epidemiological evidence identified by the ERG. Proven et al (2003) reported a maximum of 7 flares in any *single* patient based on a median follow-up of 10-years.[17] The company model predicts of a *mean* of 10.35 relapses over the same 10-year period. Similarly, Labarca et al (2015) reported a median relapse rate of 0.4 relapses/year (IQR 0.21-0.64) over a median duration of 5-years (i.e. approximately 2 relapses over 5 years compared with the company model predictions of 5.26 over the same period).[29]

Although the ERG acknowledges that the populations included in the longer-term epidemiological evidence may be more generalisable to the newly diagnosed subgroup, the marked difference in the estimates and more general concerns regarding the impact of selection bias raise important uncertainties regarding the external validity of the model estimates.

The ERG requested further clarification on the validation undertaken and additional evidence to support the external validity of the predicted number of flares. In their response, the company noted the challenges of estimating the mean number of flares given both clinical uncertainty as well as heterogeneity in the GCA population. The company also provided additional information based on the

views of attendees (rheumatologists and ophthalmologists) from an advisory board meeting. The collective view of attendees was:

- [redacted] of GCA patients would be able to taper their GC dose over approximately [redacted]
- [redacted] of GCA patients would have a relapsing/refractory GCA which required continuous titration up and down of GCs over a period of approximately [redacted]
- [redacted] of GCA patients would require a long-term GC maintenance dose for [redacted], where their GCA was controlled at a stable dose, but attempting to withdraw GC all together would cause a flare/relapse at any time after diagnosis

(Clarification response, p25)

The collective view suggests that the disease course of the majority of patients (approx. [redacted]) can be successfully managed with conventional GC tapering durations without experiencing recurrent flare/relapse. For the remaining patients [redacted] approximately [redacted] of these will experience multiple relapses requiring a longer term GC treatment duration (3-years) and the other [redacted] require long-term GC maintenance treatment (5-years or more) due to the continued risk of flare. In contrast, the company model predicts that all GCA patients receiving conventional GC treatment will eventually experience a relapse/flare. Following this relapse, the disease is then assumed to following a chronic relapse-remitting course.

The ERG acknowledges the challenges and the heterogeneity among GCA patients. However, the collective view of the attendees appears inconsistent with the characterisation of the natural history of GCA within the company model. The ERG does not consider that these uncertainties have been fully addressed in the company submission or their response. These uncertainties are further explored by the ERG in Section 6.

The company also clarified that if a patients in a flare state for consecutive assessments (e.g. week 44 and 48) that these were counted as distinct flares. The company reported that this only affects 5 patients in the 52-week GC taper arm and no patients among the TCZ-QW arm, concluded that this was unlikely to substantially impact the cost-effectiveness calculations. However, the company did not provide an additional sensitivity analysis as requested by the ERG. The ERG's review of the CSR data identified 8 possible patients that this might affect in the 52-week GC taper arm, as opposed to 5 stated by the company. The ERG is uncertain regarding the potential impact of this assumption.

Transition – GCA-related complications from relapse/flare (vision loss and stroke)

GCA-related complications were modelled as separate events that can only be experienced by patients in the relapse/flare state. The complications included were loss of vision and stroke (fatal and non-fatal). Although these complications are rare, these were considered by the company to be the most serious and relevant GCA-related complications arising as a result of a flare/relapse.

In the absence of these complications reported in the GiACTA trial, the associated risk of these were derived from a previously published economic model comparing alternative GCA diagnostic approaches.[36] Annual incidence rates of GCA-related complications at relapse/flare (0.013% for visual loss and 0.026% for stroke) were then converted to weekly probabilities in line with the model cycle length. Approximately 40% of stroke events were assumed to be major, with a 50% mortality rate.

Table 11 summarises the probabilities of GCA-related complications assigned in the model.

Table 11: Summary of probabilities of GCA-related complications

Parameter	Value	Source
Probability of visual loss at relapse/flare	0.00025	Luqmani et al, 2016[36]
Probability of stroke at relapse/flare	0.00050	Luqmani et al, 2016[36]
Probability of minor stroke at relapse/flare	0.0030	Luqmani et al, 2016[36]
Probability of major stroke at relapse/flare	0.0020	Luqmani et al, 2016[36]
Probability of death from major stroke (in addition to background mortality from life tables)	50%	Luqmani et al, 2016[36]

As previously noted, this transition assumes a surrogate relationship between GCA-related complications and relapse/flare events and that the risks of these complications are modifiable with treatment with TCZ-QW+26. Although the use of a surrogate relationship is appropriate given the rarity of these events, the degree to which these risks are modifiable with TCQ-QW remains uncertain. An editorial by Cid and Alba (2015) reported that flares mainly occur during the first 2 years after initiation of treatment and that irreversible sight loss and ischaemic complications are unusual during controlled relapses.[34] This also appears to be reflected in the responses received by the company from their clinician advisory board, who reported the risk to be of low concern generally and easily managed for patients experiencing a flare/relapse (see Clarification response, p31).

The ERG concludes that there is uncertainty regarding the extent to which these risks can be modified by treatment with tocilizumab. However, the risk of both events included in the model is so low that their inclusion is not a significant driver of the cost-effectiveness results.

Transition - GC-related AEs from all states receiving GC (fractures and diabetes)

Given the limited number of major GC-related AE events reported in the GiACTA trial, the lifetime risks of fracture and diabetes were also derived from external evidence. These risks were estimated based on cumulative GC dose measured from the GiACTA trial and subsequently extrapolated using a logistic growth regression approach. The cumulative GC dose was then linked with the risk of fracture and diabetes based on real world evidence from CPRD.[18, 37]

The calculation of cumulative GC dose for each treatment arm was undertaken in three stages:

- Stage 1 (during initial remission): based on the alternative GC tapering regimens defined in the GiACTA trial protocol.
- Stage 2 (during secondary remission): based on separate logistic growth regressions informed by the GiACTA trial data (TCZ-QW) and real world evidence from the US Market Scan Database for the 52-week prednisone tapering regimen. The separate equations assumed that the cumulative dose over time would asymptote to a total dose of [redacted] for TCZ-QW and [redacted] for 52-week prednisone taper. The equations and associated parameter inputs are reported in Table 37 (p104) of the CS.
- Stage 3 (during relapse/flare) based on separate predictive equations of the GC dose for each treatment based on the GiACTA trial data. The equations and associated parameter inputs are reported in Table 37 (p104) of the CS.

The total cumulative GC dose calculations predicted across the 3 stages were then adjusted using CPRD real world data to ensure the predictions from the model matched the cumulative GC doses reported in the CPRD data. The company noted in their response that the CPRD data lacked complete data on daily dose and hence did not have sufficient granularity to inform the logistic growth equations used in Stage 2.

Figure 9 (replicated from Figure 12 of the CS) summarises the cumulative GC dose predicted by the cost-effectiveness model over a longer time period.

Figure 9: Cumulative GC dose predicted by the company model

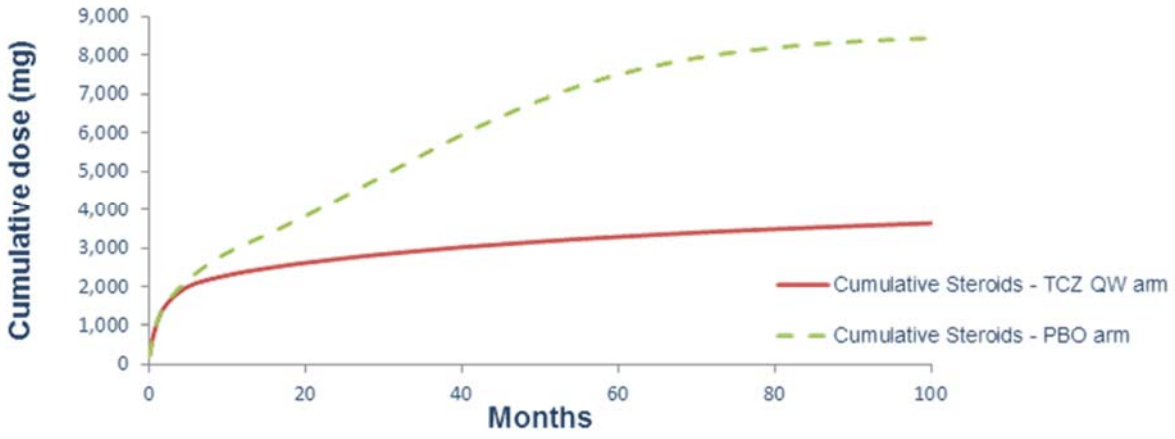


Figure replicated from CS

The ERG considers the approach to estimating cumulative dose to be reasonable and the adjustment using UK real world data increases the generalisability of the predictions. The ERG also acknowledge that the CPRD data may underestimate total GC dose as this only includes prescriptions in a primary care environment and that it was reasonable for the company to present a scenario which used the US data without further adjustment.

The ERG also notes that the same logistic growth equation and CPRD adjustment were applied across the ITT populations and subgroups. The ERG considers that the CPRD data and cumulative GC dosing is probably more reflective of the dose received for newly diagnosed patients and that higher doses, particularly in the relapsed/refractory subgroup, may be more appropriate. This issue is further explored in Section 6.

Transition - Death from any state

Estimates of background mortality applied to all states were based on 2016 UK lifetables (age and gender matched) from the Office of National Statistics, with an adjustment to avoid double counting stroke related mortality.

The ERG considers the approach to be appropriate and adequately justified by the company.

5.2.7 Health related quality of life

Remission and relapse/flare health state utilities were calculated from EQ-5D-3L (UK tariffs) data in the GiACTA trial using a mixed effects model and adjusting for baseline utility. Data were combined across all four treatment arms, given the lack of any significant differences reported between treatments and to increase the robustness of the estimates for the health state values. The company further justified this approach on the basis that the impact of a flare on a patient's quality of life was

not expected to be different across the separate arms. No time component was included as no trend in terms of utility change over time was found in the GiACTA trial data.

Table 12 summarises the main utility estimates from the mixed model for the ITT population and for the separate subgroups. The utility values estimated from the mixed model for the ITT population were 0.77 for remission and 0.64 for a relapse/flare event. The model assumes the same remission value for patients during the initial and subsequent remission periods. The lower utility estimated for a patient experiencing a relapse/flare was applied in the model for 28 days. The duration of the relapse/flare event was stated to be consistent with clinical opinion and additional analyses reported from the GiACTA trial exploring changes in utility before and after a relapse/flare.

Table 12: Summary of utilities applied to the remission and relapse states for each population

Parameter	Values for each population			Source
	ITT	Newly Diagnosed	Relapsed/Refractory	
Utility on remission	0.7713	0.8115	0.7333	GiACTA trial
Utility on flare	0.6420	0.6451	0.6343	GiACTA trial
GCA flare disutility	0.1293	0.1664	0.099	GiACTA trial

The ERG considered that the approach met the NICE reference case and that the mixed model was appropriate for the purposes of informing the model. The ERG notes that no adjustment has been made for the impact of ageing in the model and that the values for remission and flare are assumed to be constant over the entire model time horizon. However, in the absence of any significant mortality effect (i.e. other than the difference due to stroke), the ERG does not consider that this constitutes an important bias when comparing between treatment strategies in the ICER calculations.

Additional disutilities for GCA-related complications and GC-related AEs were also included and derived from the external literature. These are summarised in Table 13.

Table 13: Summary of disutilities for complications and AEs

Parameter	**Value**	**Source**
GC-related disutility	-0.07	Niederkohr and Levin 2005
GCA-related vision loss disutility from baseline	-0.36734	Luqmani et al. 2016
GCA-related minor stroke disutility from baseline	-0.17882	Luqmani et al. 2016
GCA-related major stroke disutility from baseline	-0.49122	Luqmani et al. 2016

A single GC-related disutility estimate (-0.07) is applied in the model based on an estimate reported by Niderkohr and Levin (2005).[38] This study reported the annual incidence and disutility of GC-

related adverse events based on a systematic review of previously published studies. The single GC-related distutility estimate comprises a separate 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 disutilities for less common events including fracture, psychiatric disturbance and infections which are weighted according to their incidence.

The specific disutilities and incidence of these less common events were not reported in the company submission. The ERG sourced the original values and incidence rates and a summary is presented in in Table 14. The valuation approach for each of these disutilities was not stated.

Table 14: Summary of inputs for GC-related disutility estimate

Side Effect	Disutility	Incidence (%)	Expected disutility
Base disutility	-0.03	100	-0.030
Hyperglycaemia/diabetes	-0.12	4.8	-0.006
Vertebral fracture	-0.1	6.5	-0.007
Hip/femoral fracture	-0.2	3.6	-0.007
Avascular necrosis of femoral head	-0.06	1.1	-0.001
Infection (requiring hospitalisation)	-0.19	6.7	-0.013
Peptic ulcer disease	-0.11	3.1	-0.003
Hypertension (requiring treatment)	-0.015	5.6	-0.001
Steroid myopathy	-0.05	3.4	-0.002
Psychiatric disturbance	-0.05	7.6	-0.004
Overall disutility			**-0.07**

The GC-related disutility estimate is applied for the length of the tapering period (either 26 weeks or 52 weeks) for patients in the initial remission state. Beyond the respective taper periods, no further GC-related disutility is assumed until patients experience a relapse/flare event and enter the subsequent remission state (On remission and on maintenance [escape] steroids). The GC-related disutility is then 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 the GC-related disutility for the remainder of their lifetime. The ERG considers that some of these disutilities do have potentially lifelong implications (e.g. diabetes, fracture). However, it may not be appropriate to continue to assume the base-disutility (-0.03) unless patients continue to receive lifelong treatment with GC.

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

5.2.8 Resources and costs

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

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

Table 15: Acquisition, administration and monitoring cost assumptions

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

Replicated from company submission

The submission presented separate analyses based on the list price for tocilizumab (£913.12 for 4 pre-filled syringes with 162 mg; annual cost based on QW dosing = £11,871) and the DH/PASLU approved patient access scheme (PAS cost = [redacted] for 4 pre-filled syringes; annual cost equivalent = [redacted]).

The company acknowledged that prednisolone is recommended in current guidelines and altered their costing assumptions within their revised model and base-case. The costs of GC treatment were based on the cumulative GC dose estimated for each treatment arm.

The company submission assumes no administration costs for either tocilizumab or conventional GC treatment. However, the GiACTA clinical study report (CSR) states that the first 4 subcutaneous injections of tocilizumab required administration in a setting where medications and resuscitation facilities were available and patients were required to stay for 2 hours following each injection. The CSR also states that patients and caregivers were trained to perform the subcutaneous injection at their first visit and that clinical staff could administer the injections if a patient was unable or unwilling to self-administer.

The ERG sought further clarification from the company on possible resource use and cost implications for the NHS. The company response stated that they provide a homecare delivery and Health Check service for rheumatoid arthritis (RA) patients and hospital trusts for tocilizumab, which they are looking to continue for GCA patients. The current homecare delivery service includes up to two home visits by a qualified nurse to train the GCA patient to self-administer subcutaneous tocilizumab. The company reported that there is currently a 90% uptake of homecare delivery for RA and that the remaining 10% of patients include patients collecting them personally from the hospital pharmacy and those requiring hospital-based administration. The Health Check service is provided via the telephone and comprises up to 6 calls which includes advice and counselling where required on self-administration.

The ERG was satisfied with the company responses and assuming that these services are continued for GCA patients, the administration of TCZ seems unlikely to generate significant resource use and cost implications that were not included in company model.

Monitoring for tocilizumab requires ALT and AST levels, neutrophils and platelets and lipids to be tested every 4-8 weeks. These were assumed to be included within one blood test. A cost of £3 was derived from NHS reference costs (DAPS05 directly accessed pathology service: Haematology) and applied to all patients on tocilizumab treatment every 6 weeks.

Disease management costs were estimated separately for the following health states:

- Patients 'on remission + on steroid';
- Patients 'on remission + off steroid';
- Patients 'on flare / relapse';
- Patients 'on remission + on maintenance steroids'.

Resource utilisation estimates for these states were based on data collected in the UK market research study conducted by Roche. Only limited details of this study were presented in the submission. The separate resource utilisation estimates were based on estimates of the frequency and proportion of patients expected to receive different specialist management for each state. For the different remission states, the same proportion of patients was assumed to receive care from each specialist type. However, differences in the frequency of each specialist type were assumed for the each separate remission state and for the ITT and subgroups.

Table 16 and Table 17 report the proportions and frequencies assumed by the company.

Table 16: Proportion of patients receiving specialist care in each remission state

Management Cost after diagnosis	% of patients	Cost per visit	NHS reference cost code
Rheumatologist	66%	£137	410; Rheumatology
GP	17%	£36	10.3b PSSRU 2016
Geriatrician	10%	£188	430; Geriatric Medicine
Opthalmologist	5%	£58	460; Medical Ophthalmology
Neurologist	2%	£161	400; Neurology
Other	1%	£164	300; General Medicine

Replicated from company submission

Table 17: Frequency of visits to specialist care in each remission state

Management frequency	Proportion of frequency of follow up (on remission + on steroid)			Proportion of frequency of follow up (on remission + off steroid)	Proportion of frequency of follow up (on remission + on maintenance)
	ITT	Newly Diagnosed	Relapsed/ Refractory	ITT/subgroups	ITT/subgroups
Weekly	4.6%	10.0%	4.0%	0.0%	1.9%
Every 2 weeks	14.5%	24.0%	18.0%	0.0%	9.4%
Monthly	25.9%	29.0%	29.0%	1.1%	24.5%
Every 2 months	12.7%	12.0%	14.0%	8.4%	13.2%
Every 3 months	21.0%	12.0%	22.0%	16.8%	25.9%
Every 6 months	13.0%	6.0%	9.0%	26.3%	16.5%

Replicated from company submission

The associated weekly management costs derived from the proportions and frequency estimates and applied to each state are summarised in Table 18. The ERG notes that the same weekly management costs of £26.35 were applied in the Excel model for the different populations (ITT, New-onset and Relapse/Refractory) in the 'On remission and on steroid' state, despite different frequencies reported in the previous table. The figures reported in brackets are the weekly costs estimated by the ERG based on the subgroup specific frequencies for the separate subgroups. The ERG was unclear whether this was an error or an intentional assumption made by the company. A separate deterministic sensitivity analysis has been added by the ERG at the end of this section using the subgroup specific weekly management costs for this health state.

Table 18: Weekly management costs for remission health states

Health state	Weekly management cost		
	ITT	Newly Diagnosed	Relapsed/Refractory
Patients 'on remission + on steroid'	£26.35	£26.35 (£38.41*)	£26.35 (£28.70*)
Patients 'on remission + off steroid'	£4.32	£4.32	£4.32
Patients 'on remission + on maintenance steroids'	£20.17	£20.17	£20.17

*ERG estimate

Separate proportions and frequencies were estimated for the relapse/flare state. Table 19 summarises the proportions of patients receiving care from each specialist type. The average number of appointments during the course of a flare episode was assumed to be 2.71. The weighted average cost of visits was calculated based upon the physicians involved in initial presentation and later treatment

as £259.77 in total per flare (cost of presentation = £76.11 and cost of each follow up visit = £107.40). The company also assumed that 33% of patient would receive methotrexate during the relapse/flare event.

Table 19: Proportion of patients receiving specialist care during a flare/relapse event

Management during flare	% of patients initially presenting to this speciality	% of respondents stating each physician time was involved in flare follow-up	Cost per visit	NHS reference cost code
GP	59%	44%	£36	10.3b PSSRU 2016
Rheumatologist	25%	67%	£137	410; Rheumatology [394](Department of Health 2016)(Department of Health 2016)(Department of Health 2016)
Opthalmologist	7%	10%	£58	460; Medical Ophthalmology
Geriatrician	2%	13%	£188	430; Geriatric Medicine
Neurologist	1%	6%	£161	400; Neurology
Other	7%	5%	£164	300; General Medicine

Replicated from company submission

The company submission (p121) states that "*for each resource unit cost in the economic analysis, a cost multiplier was applied to reflect that GCA patients represent high cost patients. The multiplier was calculated as 1.58 using data provided in the PSSRU 2016 by dividing the average primary care cost of the top 25% high cost patients (£381.00) over the average primary care cost of all patients (£241.00*)". The ERG notes that this multiplier does not appear to have been included within the Excel model. The reason for this discrepancy is not stated but there are several references in the submission (e.g. see response to ERG points for clarification 16) which appear to relate to assumptions and inputs included in an early model development stage and which appear to have been subsequently omitted from the final model.

The unit costs of GCA-related complications and GC-related adverse events were derived from Luqmani et al (2016) and other external sources. Table 20 summarises the unit costs. The ERG considers that these estimates appear reasonable and appropriately sourced.

Table 20: Summary of complications and adverse event costs

Event	Cost	Source
Fracture (weighted estimate based on different fracture type)	£1624 per event	Luqmani et al, 2016
Diabetes	£48.30 per week	PSSRU 2016
Vision loss- first year	£97.55 per week	Luqmani et al, 2016
Vision loss- subsequent years	£93.97 per week	Luqmani et al, 2016
Non-fatal stroke	£112.69 per week (duration =5 years)	Luqmani et al, 2016

In general, the ERG found the general presentation and reporting of the data within the submission to be difficult to follow and to validate given that the full reference to the UK market study was not provided. Further information was requested by the ERG. The company provided additional evidence and further justification which provided adequate reassurance to the ERG regarding the derivation of the numbers reported in the tables.

5.2.9 Discounting

A discount rate of 3.5% per annum was applied to both costs and outcomes in the company's base case in accordance with the NICE reference case.

5.2.10 Cost effectiveness results

As part of their clarification response, the company submitted a revised model and updated results tables. The revised submission included programming corrections requested by the ERG, alternative costing assumptions for GC (replacing the costs of prednisone with the lower acquisition costs of prednisolone) and additional subgroup analyses for newly diagnosed and relapsed/refractory GCA.

In light of the corrections and updated analyses, the ERG only reports the results presented in the revised submission and considers these to represent the relevant company base-case. In addition, since the PAS for tocilizumab already exists for other indications, the ERG only presents the PAS results and not the separate list price analysis.

The revised base-case deterministic cost-effectiveness result for the ITT population is presented in Table 21. The ICER for tociluzumab treatment with GC versus GC alone is £28,272 per additional QALY.

Table 21: Revised base-case (deterministic) cost-effectiveness results (PAS analysis)

	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	19.12	[redacted]	12.44	8.48	12.6	£12,180	0.01	0.43	£28,272
Tocilizumab with prednisone	6.52	[redacted]	12.45	8.91					

Table 22and Table 23 present disaggregated summaries of the QALY and cost data informing the ICER estimates.

Table 22: Disaggregated summary of QALY data for base-case

	Tocilizumab	**Prednisone**	**Increment tocilizumab vs Prednisone**		
			Increment	Absolute Increment	% Absolute Increment
On Remission	8.66	7.80	0.86	0.86	200%
On Flare	0.26	0.71	-0.45	0.45	-104%
GCA-related complications	-0.01	-0.03	0.02	0.02	4%
Total QALYs	8.91	8.48	0.43	0.43	100%

The disaggregated QALY data highlights that the main driver of incremental QALY gains is the additional time patients are assumed to be in one of the remission states with tocilizumab treatment. The impact of differences due to GCA-related complications is minor. The QALY gains are conferred via two main sources: (i) a longer time to first flare which means that patients receive the higher utility of remission and avoid the utility decrement of GC-related AEs; (ii) fewer subsequent relapse/flare events meaning that a higher proportion of time, following an initial relapse/flare, is spend in the subsequent remission state.

Table 23: Disaggregated summary of cost data for base-case

	Tocilizumab	Prednisone	Increment tocilizumab vs Prednisone		
			Increment	Absolute Increment	% Absolute Increment
Tocilizumab cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flare costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCA related costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions based on 1,000 simulations. The probabilistic base-case ICER reported by the company for the ITT population is £30,579 per QALY. The associated cost-effectiveness plane and acceptability curves were also presented. The probability that tocilizumab with GC is cost-effective at a threshold value of £30,000 per additional QALY is 0.59 compared with GC alone.

The ERG considers that the probabilistic ICERs represent the most appropriate estimates for the purposes of decision making. The probabilistic ICER is higher than the deterministic estimate, indicating that there are non-linearities in the model that should be accounted for in the mean ICER estimates. However, the ERG was unable to replicate the company probabilistic ICER estimates. The magnitude of variation between the company and the ERG's estimates (reported in detail in Section 6) also exceeded that which could be explained by the use of different random number sets.

The company did not separately present the mean cost and QALY estimates from the probabilistic analysis and hence the ERG could not validate or check the separate calculations informing the ICER estimates. However, the ERG believes that the company may have incorrectly calculated the probabilistic ICER by using an estimate derived from mean of the ICERs conducted within each simulation of the PSA. This approach is incorrect as the correct probabilistic ICER is the ratio based on the mean cost and QALYs derived across the simulations and not the mean ICER ratio. When calculated appropriately, by dividing the mean incremental cost across the PSA simulations by the mean incremental QALYs across the PSA, the ERG found the probabilistic ICER to be lower than the deterministic ICER (£26,748 vs £28,272 per QALY).

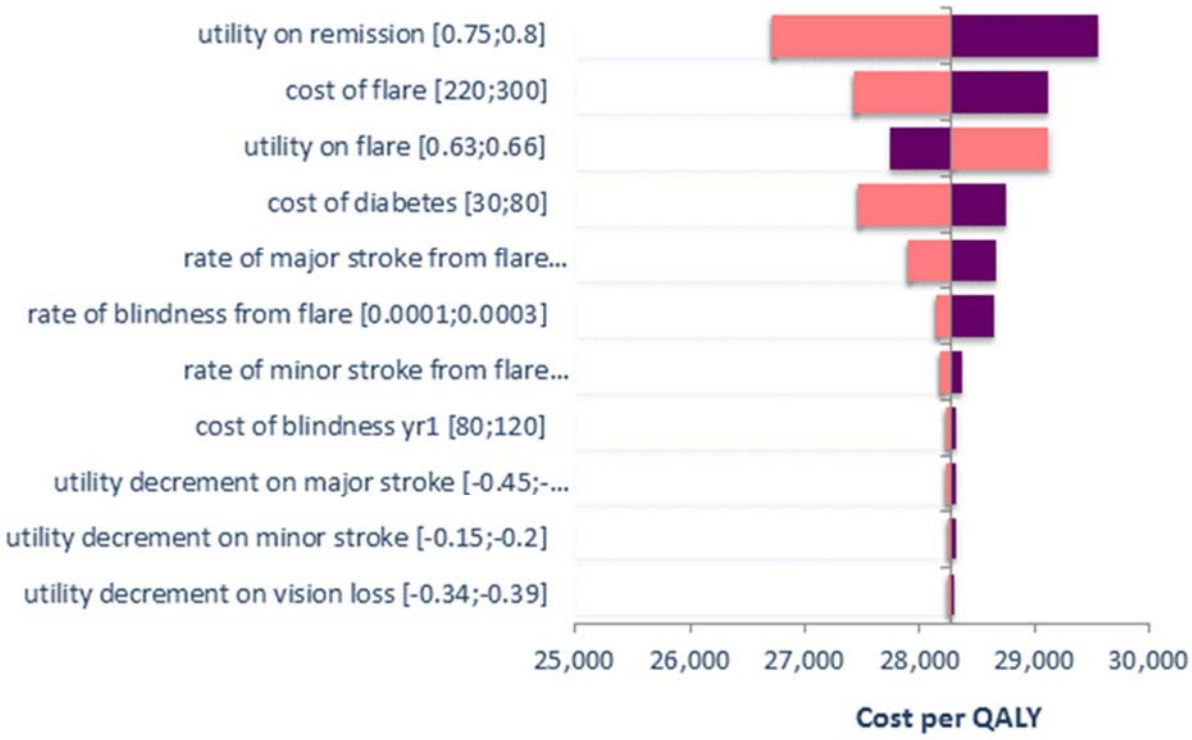
The company also provided probabilistic ICER results within their response. However, the same probabilistic ICER results reported for the ITT population (£30,579) were presented for each subgroup. Given the concerns previously noted regarding the inability to replicate the probabilistic ICER for the ITT population, the ERG presents revised probabilistic estimates for each population in Section 6.

Deterministic sensitivity analysis

The company presented a series of univariate deterministic sensitivity analyses for the ITT population to assess the impact of varying key model input parameters on the ICER. The univariate analyses were conducted by varying individual parameters across their lower and upper values based on the 10th and 90th percentile from the probabilistic distributions assigned.

Figure 10 shows a tornado diagram summarising the most influential parameters reported by the company.

Figure 10: Tornado diagram (PAS price)



CS, Figure 25 (updated sections)

The tornado diagram shows minimal variation in the ICER across the individual parameters. The highest variation was reported for the utility value assigned to the remission state with an associated ICER range between £26,711 and £29,553 per QALY. The ERG considers that it would have been

more appropriate to have used the associated 95% confidence intervals to inform the lower and upper values (i.e. 2.5th and 97.5th percentiles from the probabilistic distributions rather than the 10th and 90th percentiles) and that the results underestimate the uncertainty associated with individual parameters.

Scenarios

A range of scenario analyses were also undertaken. The alternative scenarios were presented in the CS within two separate sets of analyses. The first set of analyses assessed the use of alternative parametric models for the time to first flare and alternative stopping rules for tocilizumab (reported in Table 54, CS). The second set of analyses referred to additional scenarios considered relevant to the appraisal relating to the clinical validity and sensitivity of the inputs chosen for the base case (reported in Table 56, CS). These additional scenarios included the impact of alternative assumptions for age, the duration of tocilizumab treatment and the mean cumulative dose and variation in the rate of subsequent flares.

Table 24 summarises the results from the key scenarios across the two sets of analyses. The scenarios show that the base-case ICER appeared most sensitive to the assumptions regarding the treatment duration period and the use of the same parametric model for the time to first flare for tocllizumab as assumed for GC alone.

Table 24: Summary of key scenario analysis results – ITT population

Scenario	Scenario	Brief rationale	Impact on base-case ICER
Base case			£28,272
Age	73	Based on real world data (CPRD)	£33,159
Fixed duration of tocilizumab treatment	12 months 36 months	Uncertainty in the treatment duration period	£7,767 £47,763
Annual reduction in re-flare rate	5% 10%	Variation in the rate of re-flare reported in clinical studies	£33,902 £37,997
Mean GC cumulative dose	14g	CPRD mean dose may be underestimating actual dose due to lack of secondary care prescriptions	£25,695
Alternative parametric model (time to first flare – tocilizumab)	Exponential	Most extreme approach	£46,418

Adapted from company submission

Subgroups

Additional results were provided by the company for the newly diagnosed and relapsed/refractory subgroups as part of their response to the points for clarification. Deterministic results are provided in Table 25 and Table 26.

The ICER results were less favourable for the newly diagnosed subgroup (£37,334) and more favourable for the relapsed/refractory subgroup (£22,403), compared to the base-case ICER results for the ITT population (£28,272). The differences in the ICER estimates across the populations are driven largely by the incremental difference in the number of flares. The incremental difference in the number of flares was estimated to be -5.87 in the newly diagnosed and -19.21 in the relapsed/refractory subgroups, compared to -12.24 in the base-case ITT population. The differences across the different populations arise due to different parametric functions for the time to first flare and different rates of subsequent relapse/flare events.

Table 25: Deterministic cost-effectiveness results – Newly diagnosed 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	14.48	[redacted]	12.45	9.02	-5.87	£13,202	0.00	0.35	£37,334
Tocilizumab with prednisone	8.61	[redacted]	12.45	9.38					

Table 26: Deterministic cost-effectiveness results – 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	25.59	[redacted]	12.84	8.24	-19.21	£10,993	0.01	0.49	£22,403
Tocilizumab with prednisone	6.38	[redacted]	12.85	8.73					

Although separate scenario analyses were not presented in the company response for these subgroups, the ERG has repeated the same key scenarios presented for the ITT population for each subgroup. The results are summarised in Table 27 and Table 28.

Table 27: Summary of key scenario analysis results (ERG analysis) – Newly diagnosed subgroup

Scenario	Scenario	Brief rationale	Impact on base-case ICER
Base case			£37,334
Age	73	Based on real world data	£42,581
Fixed duration of tocilizumab treatment	12 months 36 months	Uncertainty in the treatment duration period	£12,354 £61,080
Annual reduction in re-flare rate	5% 10%	Variation in the rate of re-flare reported in clinical studies	£41,524 £44,450
Mean GC cumulative dose	14g	CPRD mean dose may be underestimating actual dose due to lack of secondary care prescriptions	£34,519
Alternative parametric model (time to first flare – tocilizumab)	Exponential	Most conservative approach	£71,693

Table 28: Summary of key scenario analysis results (ERG analysis) – Relapsed/refractory subgroup

Scenario	Scenario	Brief rationale	Impact on base-case ICER
Base case			£22,403
Age	73	Based on real world data	£28,093
Fixed duration of tocilizumab treatment	12 months 36 months	Uncertainty in the treatment duration period	£4,363 £39,577
Annual reduction in re-flare rate	5% 10%	Variation in the rate of re-flare reported in clinical studies	£28,708 £33,395
Mean GC cumulative dose	14g	CPRD mean dose may be underestimating actual dose due to lack of secondary care prescriptions	£20,260
Alternative parametric model (time to first flare – tocilizumab)	Exponential	Most conservative approach	£34,531

As noted in Section 5.2.8, the subgroup results reported by the company apply the same weekly management costs of £26.35 were applied in the Excel model for the different populations (ITT, Newly Diagnosed and Relapse/Refractory) in the 'On remission and on steroid' state, despite different frequencies reported. The ERG undertook a separate deterministic sensitivity analysis based on the different frequencies reported by the company. The results of these are presented in Table 29.

Table 29: ERG revised results based on alternative weekly management costs for remission health states

Weekly management cost for patients 'on remission + on steroid'		ICER	
Newly diagnosed	Relapsed/Refractory	Newly diagnosed	Relapsed/Refractory
£38.41*	£28.70*	£35,797	£22,253

*ERG estimate

5.2.11 Model validation and face validity check

The model was developed in-house by Roche and the face-validity of the model structure and assumptions were reported to have been reviewed by independent clinical and health economic experts. Internal validation was undertaken by an independent, external agency that performed checks on the technical programming and examined the model to identify possible logical errors or common sense issues. The external validity of the model results were also stated to have been validated by clinical opinion with explicit reference made to the re-flare rate and the proportion of patients on maintenance steroid therapy over time.

The ERG notes that while the company provided a summary of the validation steps undertaken, there was only limited detail reported in the submission on the processes and results of these validation activities. The ERG performed a series of their own independent checks of the technical programming and undertook a series of basic logical checks (e.g. altering specific inputs to determine whether the results altered in line with expectations, setting utilities to 1 to ensure that LY and QALY differences were equal etc.) to identify possible logical errors.

The ERG's logical checks identified an important error in the QALY calculations which was corrected by the company and a revised model and full set of results were provided by the company. Several other issues and concerns were also addressed by the company in their response and have been described in detail in earlier sections.

Although the ERG is satisfied with the internal validity of the model, significant uncertainties remain regarding the clinical and external validity of the longer-term extrapolations and the extent to which the current model appropriately characterises the natural history of GCA.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. However, the ERG identified a number of key uncertainties and potential errors in the CS. Several of these were subsequently addressed by the company in their response document. However, the ERG identified a number of key issues and areas of remaining uncertainty, including:

1. *Inability to replicate the probabilistic ICERs reported in the CS*

The ERG considers that the probabilistic ICERs represent the most appropriate estimates for the purposes of decision making. The ERG was unable to replicate the company's probabilistic ICER estimates and was not presented with the separate calculations used to estimate these. The estimates reported for the subgroups were also not correct.

2. *The duration of treatment and the assumption that the benefits of tocilizumab continue over a lifetime*

A key assumption applied in the base-case analysis is that the efficacy of tocilizumab over longer treatment durations will follow the same trend as observed in the within-trial period and maintained over a lifetime. Uncertainty related to the duration of treatment was explored using scenarios evaluating alternative fixed durations of tocilizumab treatment between 12 and 60 months. However, these scenarios only considered the cost implications of alternative treatment durations. The ERG considers that these scenarios do not represent the full extent of uncertainty in the cost-effectiveness results since the same efficacy is assumed within each scenario. The ERG also does not consider that the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration is adequately justified or evidence based.

3. *Uncertainty concerning the choice of parametric survival models and use of different model types*

The ERG notes that no additional justification was provided by the company for using different types of parametric model based on the time to first flare. The ERG also had important concerns regarding the external validity of the longer-term predictions.

4. *Uncertainty concerning the rate of subsequent relapse/flares following an initial flare*

The CS assumes that these transition probabilities are constant over time suggesting that patients remain at ongoing risk of further flares for the remainder of their lifetime. The mean number of flares (19.67) predicted by the model over a 30-year period appears high for the prednisone alone comparator based on longer-term epidemiological evidence identified by the ERG. The use of a post-randomised subset also introduces an important source of selection bias which will impact on the validity of the longer term predictions.

Although the ERG acknowledges the challenges and the heterogeneity among GCA patients noted by the company, the ERG considers that the characterisation of the natural history of GCA and the ongoing recurrent risk of subsequent flares appears does not appear to be supported by external

evidence or the collective view of expert clinicians advising the company. The ERG does not consider that these uncertainties have been fully addressed in the scenarios presented by the company.

5. *Uncertainty regarding the generalisability of the GiACTA trial to clinical practice in England and Wales*

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.

Although the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, there remains uncertainty surrounding the generalisability of this tapering regimen and the associated relapse rate to a longer tapering regimen (18-24 months) more conventionally used in clinical practice.

Given the importance of a number of these issues, additional analyses independently undertaken by the ERG are presented in Section 6, which consider the potential impact of the remaining uncertainties on the cost-effectiveness results.

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

6.1 Overview

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

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

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

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

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

The ERG revised probabilistic ICERs are: £26,748 (ITT population); £37,036 (new-onset) and £21,102 (relapsed-refractory). The probability that tocilizumab treatment is cost-effective at a threshold value of £30,000 per additional QALY is 0.61 (ITT population), 0.40 (new-onset subgroup) and 0.73. (relapse/refractory subgroup) compared with GC treatment alone.

Table 30: ERG revised base-case probabilistic ICER results - ITT population

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

Table 31: ERG revised probabilistic ICER results - New onset 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	15.28	[redacted]	12.42	8.97	-5.97	£13,076	0.01	0.37	£35,766
Tocilizumab with prednisone	9.32	[redacted]	12.43	9.33					

Table 32: ERG revised probabilistic ICER results - 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	26.45	[redacted]	12.82	8.19	-19.11	£10,895	0.03	0.52	£21,000
Tocilizumab with prednisone	7.34	[redacted]	12.85	8.70					

6.3 Additional ERG analyses

Although the ERG is satisfied with the internal validity of the model, significant remaining uncertainties were identified in Section 5 concerning the external validity of the longer-term extrapolations and the extent to which the current model appropriately characterises the natural history of GCA.

A series of additional scenarios were undertaken to assess the impact of these additional uncertainties and to inform an alternative ERG base-case. The alternative ERG base-case is presented in Section 6.4.

6.3.1 Scenario 1: Duration of tocilizumab treatment and benefits

The assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration period does not appear to be adequately justified or evidence based. An important limitation of the company base-case is the absence of any structural link between the treatment duration period and the effectiveness inputs. Consequently, the same effectiveness assumptions are employed across the separate treatment duration periods and only differences in treatment costs are assumed within the scenario analyses presented.

The longer term benefits of tocilizumab are driven by two main assumptions: (i) the continued use of treatment specific and different types of parametric functions over the entire extrapolation period for the time to first flare; and (ii) the continued use of treatment specific weekly rates of further relapse/flare events in the subsequent remission state.

The ERG notes that the model submitted by the company incorporates additional flexibility to make alternative assumptions concerning ongoing benefits beyond the treatment duration period. Additional functionality is provided in the model which allows the user to set the length of treatment duration benefit post-discontinuation of tocilizumab treatment. Within the Excel model this is reported as a 'treatment waning' parameter, allowing the user to set the length of the treatment duration benefit (in months) period post-discontinuation. The company base-case and separate scenarios set this number to a sufficiently high number (999) so that no waning of effect is assumed.

The 'treatment waning' parameter provides a potential structural link between treatment duration and benefits. At the time point at which waning is applied, patients who had previously received tocilizumab are assumed to revert to the equivalent risks as faced by patients previously treated with GC alone, albeit with different risks applied depending on whether patients are in the initial or subsequent remission state.

In the absence of robust evidence supporting a continuing effect of tocilizumab beyond the treatment period, the ERG considers that it is more appropriate to set the treatment duration benefit post-continuation to 0, such that that the longer term QALY benefits of tocilizumab treatment are more closely related to the differences predicted during treatment duration period itself.

It is important to appreciate that incorporating the waning assumption in this way does not mean that the health outcomes and costs of the alternative treatment strategies are identical in the period following discontinuation of tocilizumab treatment. Instead, the approach assumes that the differences between strategies in the post-discontinuation period arise from continuing prognostic differences due to the different distribution of patients in initial and subsequent remission health states. Since lower risks of relapse/flare events are assigned to the initial remission state compared with the subsequent remission state, the higher proportion of patients predicted to still be in the initial remission state over the treatment duration period with tocilizumab will lead to ongoing prognostic benefits in the post-treatment duration period.

The first scenario presented by the ERG (Scenario 1a) sets the treatment duration benefit post-continuation to 0 and hence applies the same risks estimated for GC patients to patients who previously received tocilizumab, depending on the state they reside at the end of the treatment period

(i.e. same exponential function for patients still in the initial remission and same weekly relapse rate for patients in the subsequent remission state).

Full probabilistic ICER results tables are presented in Table 33 (ITT population), Table 34 (newly diagnosed) and Table 35 (relapsed/refractory) for the 2-year fixed treatment duration period.

Table 33: ERG scenario 1a results - ITT population

	Total estimates				Incremental estimates				
Technologies	**Total Flares**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incr. Flares**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER (£/QALY)**
Prednisone alone	20.13	[redacted]	12.42	8.44	-1.52	£15,992	0.00	0.12	£134,241
Tocilizumab with prednisone	18.61	[redacted]	12.43	8.55					

Table 34: ERG scenario 1a results - New-onset 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	15.27	[redacted]	12.38	8.94	-0.92	£15,977	0.00	0.10	£156,302
Tocilizumab with prednisone	14.35	[redacted]	12.38	9.05					

Table 35: ERG scenario 1a results - 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	26.28	[redacted]	12.80	8.18	-2.05	£15,935	0.01	0.12	£127,529
Tocilizumab with prednisone	24.23	[redacted]	12.81	8.30					

The ERG probabilistic ICERs for scenario 1a are: £134,241 (ITT population); £156,302 (newly diagnosed subgroup) and £127,529 (relapsed-refractory subgroup) per QALY. Across the alternative treatment duration periods, the probabilistic ICERs ranged between: £112,806 - £166,270 (ITT population); £124,168 - £196,680 (newly diagnosed) and £108,558 - £153,437 (relapsed/refractory) per QALY.

Table 31 provides a summary for the alternative durations (between 1 to 5 years) considered in the company's scenario analysis.

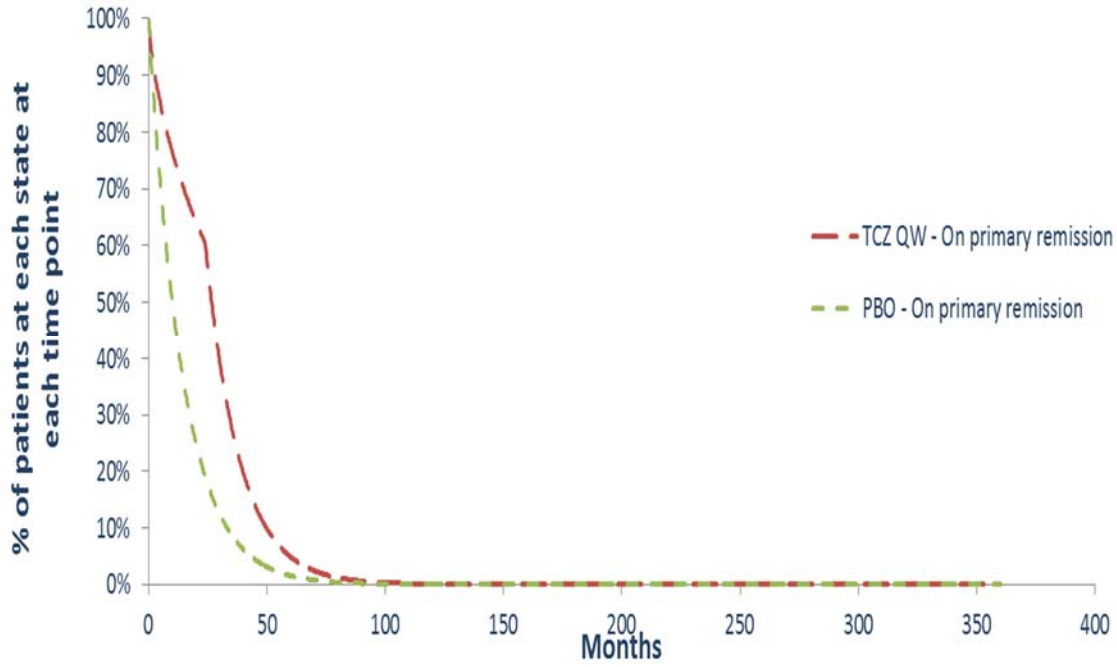
Table 36: ERG scenario 1a results - Alternative durations

	Population					
	ITT		Newly diagnosed		Relapsed/refractory	
Duration	**Incr. Flare**	**ICER**	**Incr. Flare**	**ICER**	**Incr. Flare**	**ICER**
12 months	-0.72	£112,806	-0.46	£124,168	-0.98	£108,558
24 months	-1.51	£139,122	-0.92	£156,302	-2.05	£127,529
36 months	-2.26	£147,668	-1.40	£170,429	-3.10	£138,992
48 months	-2.95	£156,573	-1.79	£181,979	-4.16	£146,923
60 months	-3.73	£166,270	-2.17	£196,680	-5.12	£153,437

The results of scenario 1a show how sensitive the ICER results are to the waning-assumption. The differences are largely driven by the much smaller incremental difference in the estimated number of flares. However, while the ERG considers that setting the treatment duration benefit post-discontinuation to 0 is more appropriate than continuing to assume treatment specific differences, the manner in which this is implemented within this scenario seems to further compound the ERG's concerns regarding the clinical plausibility and external validity of the results for GC alone. Specifically, the concerns noted regarding the high number of flares predicted now applies to both treatment strategies.

Figure 11**Error! Reference source not found.** shows the implications for the ITT population of assuming a common parametric function for time to first flare from the point of treatment discontinuation, based on the exponential distribution used for GC alone. While the figure shows that continuing benefits are achieved post-discontinuation, the area between the curves is greatly reduced compared to the base-case analysis. More importantly, the ERG's concerns regarding the external validity of longer term predictions made for GC alone now also apply to the longer term predictions of tocilizumab. That is, a significantly higher proportion of patients are assumed to relapse and over a much shorter follow-up period compared to external epidemiological evidence.

Figure 11: Longer-term parametric extrapolation of time to first flare (ITT population): Scenario 1a



In Section 5, the ERG concluded that the future trajectory of patients in the GC alone arm beyond 52-weeks is likely to follow a different trend than the period up to 52-weeks. This is because the period up to 52-week covers the entire duration of the tapering period and represents the period over which patients are at highest risk of a relapse/flare event. The ERG questioned the relevance of this period as the basis for projecting the future probability of flare in patients who have successfully completed their taper regimen with GC alone and without experiencing a flare.

Given these concerns, the ERG considers that a more appropriate assumption would be to assume the same common parametric function for time to first flare from the point of treatment discontinuation, but to base this on the Weibull distribution from the tocilizumab arm rather than the exponential distribution from the GC alone arm. The justification for this is that the Weibull distribution is based on a decreasing risk which appears consistent with longer term epidemiological data. Furthermore, data from the tocilizumab arm may provide a better basis for subsequent projections of the future risk of GC patients who have been successfully tapered and not experienced a relapse/flare. This is because the Weibull distribution based on the tocilizumab data is informed by larger numbers of patients who: (i) didn't experience a relapse/flare and (ii) experienced longer-periods of time following the successful withdrawal of steroid treatment.

Therefore the ERG undertook a further scenario (Scenario 1b) where, at the point of tocilizumab discontinuation, patients in the GC alone treatment strategy are switched to the same Weibull function

used for tocilizumab. The results of this scenario are presented in Table 37, Table 38 and Table 39. The ERG probabilistic ICERs for scenario 1a are: £32,661(ITT population); £44,338 (newly diagnosed subgroup) and £23,730 (relapsed-refractory subgroup) per QALY.

Table 37: ERG scenario 1b results - ITT population

	Total estimates				Incremental estimates				
Technologies	**Total Flares**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incr. Flares**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER (£/QALY)**
Prednisone alone	18.73	[redacted]	12.40	8.50	-10.95	£12,156	0.02	0.37	£32,661
Tocilizumab with prednisone	7.78	[redacted]	12.42	8.87					

Table 38: ERG scenario 1b results - New-onset 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	14.09	[redacted]	12.10	8.81	-5.16	£12,604	0.01	0.28	£44,338
Tocilizumab with prednisone	8.93	[redacted]	12.11	9.10					

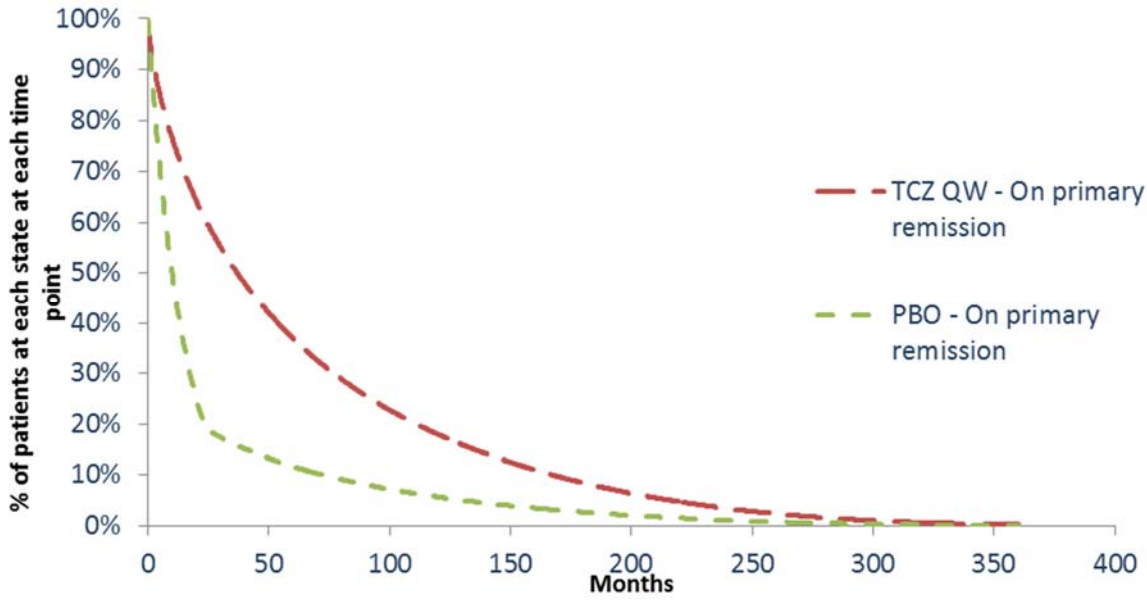
Table 39: ERG scenario 1b results - Relapsed/refractory subgroup

	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	24.55	[redacted]	12.42	7.98	-17.42	£10,572	0.03	0.45	£23,730
Tocilizumab with prednisone	7.13	[redacted]	12.45	8.43					

Figure 12 shows the implications in the ITT population of assuming a common parametric function for time to first flare from the point of treatment discontinuation, based on the Weibull distribution used for tocilizumab treatment. Although the switch between the 2 functions creates an unrealistic kink in the survival function, the ERG considers that Scenario 1b represents a more clinically

plausible trajectory for patients receiving GC alone, with a higher proportion of patients assumed to remain in remission over a longer.

Figure 12: Longer-term parametric extrapolation of time to first flare (ITT population): Scenario 1b



The ERG notes that while this approach provides a more realistic projection for GC alone, the switch between distributions is based on an assumption of a 2-year treatment period with tocilizumab treatment. This means that the trajectory of GC alone patients is switched at 2 years i.e. 1 year after successful tapering. This means that extrapolation of the period between 12-24 months for GC alone is still being informed by data from a period over which patients are at higher risk. Consequently there remains significant uncertainty regarding the appropriate shape of the parametric distribution over longer-periods and the relevant time period over which the shapes may differ (i.e. during the initial tapering period and post tapering).

6.3.1 Scenario 2: The probability of subsequent flare

While the ERG considers that Scenario1b provides a more appropriate assumption for informing longer term projections of the time to first flare, the overall mean relapse rate remains high and appears inconsistent with longer-term epidemiological evidence identified by the ERG. In Section 5, the ERG also identified several concerns regarding the approach and assumptions used by the company to inform the transition probabilities from the remission (escape) state to subsequent relapse/flare. These concerns relate to possible selection bias and the external validity of the total number of flares predicted for the GC alone strategy.

Although several references reporting longer-term relapse data were identified by the ERG, only one study was identified which reported an annualised relapse rate over a longer time horizon. The study by Larbaca et al (2016) reported a median rate of 0.4 relapses per year (IQR 0.21-0.64) over a median duration of 5-years follow-up. The study was a retrospective cohort study of 286 patients with biopsy-proven GCA from 1998 to 2013.

The ERG considers that this study provides a useful basis to assess the external validity of the company estimates and for potentially informing the estimate of the weekly probability of flare applied to the flare state for patients receiving GC alone. A separate scenario (Scenario 2) was conducted by the ERG using this external source.

In study by Larbaca et al, patients were followed up from the point of diagnosis. Consequently, the annual relapse rate reported (0.4 per year) appear most relevant to the newly diagnosed subgroup. A series of adjustments and assumptions were made by the ERG to generalise the data across the separate populations to inform the ERG's scenario analysis:

1) A weekly probability of 0.0076 was estimated based on the annual rate of 0.4 reported. This was assumed to represent the probability of flare for the newly diagnosed subgroup for patients receiving GC alone.

2) A relative hazard between subgroups was estimated by the ERG based on the relapse rates reported for GC alone in the GiACTA trial between the newly diagnosed and the ITT and relapsed/refractory populations. This relative hazard was then applied to the annual rate of 0.4 in order to estimate equivalent rates for the ITT and relapsed/refractory populations for GC alone.

3) The relative hazards between tocilizumab treatment and GC alone were then estimated from the GiACTA trial data and applied to the population specific relapse rates estimated for GC alone. However, rather than using subgroup specific hazard ratios, the ERG used the overall ITT relative hazard for all populations, noting concerns previously highlighted in Section 5 regarding the clinical plausibility of the subgroup relative effects.

4) Weekly probabilities for each population for TCZ QW+26 and GC alone were then estimated.

Table 40 provides a comparison of the alternative ERG estimates (based on external data and GiACTA trial data) for the weekly probability of flare applied to the subsequent remission and those used in the company submission (based entirely on the GiACTA trial data).

Table 40: Comparison of weekly probability of flare applied to the subsequent remission state

Population	Treatment arm	Mean rate (in log scale)	Weekly probability of flare: ERG	Weekly probability of flare: Company
ITT	Tocilizumab QW	-1.36928	0.0049	0.0106
	Placebo 52 week	-0.59736	0.0105	0.0228
Newly diagnosed	Tocilizumab QW	-1.68821	0.0035	0.0127
	Placebo 52 week	-0.91629	0.0076	0.0166
Relapsed/ Refractory	Tocilizumab QW	-1.14328	0.0061	0.0083
	Placebo 52 week	-0.37136	0.0131	0.0285

The weekly probabilities estimated by the ERG are lower than those used in the company base-case. Importantly the ERG estimates are also logically consistent across the subgroups (i.e. the weekly probability for TCZ QW+26 is higher in the relapsed/refractory subgroup compared to the ITT and newly diagnosed populations).

Full probabilistic ICER results tables are presented in Table 41 (ITT population), Table 42 (newly diagnosed) and Table 43 (relapsed/refractory) for a 2-year fixed treatment duration period with tocilizumab. The ERG probabilistic ICERs for scenario 2 are: £39,579 (ITT population); £41,322 (newly diagnosed subgroup) and £37,582 (relapsed-refractory subgroup) per QALY.

Table 41: ERG scenario 2 results - ITT population

	Total estimates				Incremental estimates				
Technologies	Total Flares	Total costs (£)	Total LYG	Total QALYs	Incr. Flares	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Prednisone alone	9.58	[redacted]	12.44	8.61	-5.62	£13,371	0.01	0.34	£39,579
Tocilizumab with prednisone	3.95	[redacted]	12.45	8.95					

Table 42: ERG scenario 2 results - Newly diagnosed

	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	7.15	[redacted]	12.42	9.12	-4.07	£13,440	0.01	0.33	£41,322
Tocilizumab with prednisone	3.09	[redacted]	12.43	9.44					

Table 43: ERG scenario 2 results - Relapsed/refractory

	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	12.28	[redacted]	12.81	8.36	-7.34	£13,084	0.01	0.35	£37,582
Tocilizumab with prednisone	4.93	[redacted]	12.82	8.71					

The ERG considers that Scenario 2 provides lower and more clinically plausible estimates of the mean number of flares over a patient's lifetime.

6.3 ERG alternative base-case

The assumptions and approaches applied by the ERG for scenarios 1b and 2 were combined and used as part of an ERG alternative base-case. Two further amendments are also proposed within the ERG alternative base-case:

1. A mean age of 73 years is assumed based on the UK CPRD data source on the basis that this more appropriately reflects the real world clinical population in England and Wales.
2. The ERG considers that the CPRD data and cumulative GC dosing is probably more reflective of the dose received for newly diagnosed patients and that higher doses, particularly for the relapsed/refractory subgroup, may be more appropriate. Therefore, the ERG excluded the CPRD adjustment applied to cumulative GC dosing for the relapsed/refractory subgroup

The results of the ERG alternative base-case for a fixed 2-year duration period for tocilizumab treatment are presented in Table 44, Table 45 and Table 46. The ERG probabilistic ICERs for are:

£65,801(ITT population); £73,046 (newly diagnosed subgroup) and £58,411 (relapsed-refractory subgroup) per QALY.

Table 44: ERG alternative base-case results (2-year treatment duration) - ITT population

	Total estimates				Incremental estimates				
Technologies	**Total Flares**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incr. Flares**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER (£/QALY)**
Prednisone alone	7.56	[redacted]	10.76	7.51	-1.68	£14,110	0.00	0.21	£65,801
Tocilizumab with prednisone	5.88	[redacted]	10.77	7.72					

Table 45: ERG alternative base-case results (2-year treatment duration) – Newly diagnosed 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	5.50	[redacted]	10.51	7.78	-1.10	£13,748	0.00	0.19	£73,046
Tocilizumab with prednisone	4.40	[redacted]	10.51	7.97					

Table 46: ERG alternative base-case results (2-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	9.10	[redacted]	10.46	6.88	-2.18	£12,967	0.00	0.22	£58,411
Tocilizumab with prednisone	6.92	[redacted]	10.46	7.10					

Although the ERG considers that their revised base-case addresses several key areas of uncertainties, the remains significant uncertainty regarding the appropriate duration of treatment with tocilizumab. Both the company and ERG alternative base-case assume a fixed 2-year treatment period for tocilizumab. However, the scenarios presented by both the ERG demonstrate that the cost-effectiveness of continued use of tocilizumab beyond the 52-week period reported in the GiACTA

trial are significantly influenced by the uncertainty and assumptions made concerning the ongoing efficacy of TCZ-QW over longer treatment durations.

Inevitably, until longer-term evidence is available these uncertainties will remain. However, the ERG considered that a further set of results based on a 1-year treatment duration would provide useful additional information to inform the committee's deliberations. Specifically, this provides the most internally valid approach consistent with the treatment duration period assessed in the GiACTA trial with extrapolations based on the longer-term implications of differences in effectiveness reported over this observed follow-up period.

The ERG alternative base-case was repeated for a 1-year treatment duration period. However, the common parametric function for time to first flare (based on the Weibull distribution used for tocilizumab treatment) was applied based at 1-year treatment discontinuation.

The results of the ERG alternative base-case for a fixed 1-year duration period for tocilizumab treatment are presented in Table 47, Table 48 and Table 49. The ERG probabilistic ICERs for are: £36,960 (ITT population); £41,577 (newly diagnosed subgroup) and £30,158 (relapsed-refractory subgroup) per QALY. The more favourable ICER results compared to the 2-year treatment duration period are driven by the lower acquisition costs of tocilizumab over a shorter treatment period which reduces the incremental differences in total costs to a greater degree than the reduction in the incremental QALY differences.

Table 47: ERG alternative base-case results (1-year treatment duration) – ITT population

	Total estimates				Incremental estimates				
Technologies	**Total Flares**	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incr. Flares**	**Incr. costs (£)**	**Incr. LYG**	**Incr. QALYs**	**ICER (£/QALY)**
Prednisone alone	6.98	[redacted]	10.73	7.55	-1.03	£5,296	0.00	0.14	£36,960
Tocilizumab with prednisone	5.95	[redacted]	10.74	7.70					

Table 48: ERG alternative base-case results (1-year treatment duration) - Newly diagnosed 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	5.16	[redacted]	10.57	7.89	-0.65	£5,172	0.00	0.12	£41,577
Tocilizumab with prednisone	4.51	[redacted]	10.58	8.01					

Table 49: ERG alternative base-case 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					

6.4 Conclusions from ERG analyses

A series of additional revisions and alternative assumptions were explored by the ERG using two main scenarios. These scenarios addressed uncertainties related to: (i) the duration of treatment and the assumption that the benefits of tocilizumab continue over a lifetime; (ii) uncertainty concerning the choice of parametric survival models for time to first flare and use of different model types and (iii) uncertainty concerning the rate of subsequent relapse/flares following an initial flare. Within these scenarios, the ERG proposed alternative assumptions and data sources which they considered had greater face validity and were more consistent with the natural history of GCA reported in longer-term epidemiological studies. These alternative approaches and data sources were then combined as part of an alternative ERG base-case analysis.

The ERG's alternative base-case presented results for alternative treatment duration periods between 1 and 2 years. The ERG ICER results were higher than those reported by the company. The ERG probabilistic ICERs for a 2-year treatment period were: £65,801(ITT population); £73,046 (newly diagnosed subgroup) and £58,411 (relapsed-refractory subgroup) per QALY. The ERG probabilistic ICERs for a 1-year treatment period were: £36,960 (ITT population); £41,577 (newly diagnosed subgroup) and £30,158 (relapsed-refractory subgroup) per QALY.

The ERG considers that the 1-year treatment period results provide the most internally valid estimates consistent with the treatment duration period assessed in the GiACTA trial. However, in the absence of a clear stopping rule for tocilizumab there remains significant uncertainty concerning the appropriate duration of tocilizumab treatment. The differences reported between the company and ERG highlight that important uncertainties remain concerning the optimal duration of tocilizumab treatment and the associated longer-term benefits.

7 End of life

Within this section, the ERG critiques relevant information regarding whether the intervention is likely to meet the end of life criteria published by NICE. It is recognised that this will be decided by the relevant NICE appraisal committee and this section may have no bearing upon their decision.

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;

In the context of this assessment the end of life criteria are not applicable.

8 Overall conclusions

Evidence from a large, reasonably good quality RCT demonstrates the effectiveness of tocilizumab in achieving sustained remission, reducing the risk of flares, and reducing the GC burden. However, the treatment effect in new-onset vs relapsing patients was not fully explored, nor was the effect in patients with GCA vs LV or both. The generalisability of the trial is uncertain due to the age of patients, the ratio of cranial vs LV GCA patients, and the uncertainty regarding the taper that will be used with tocilizumab in practice

The available preliminary evidence indicates that around 30% of patients will flare once tocilizumab treatment is stopped: for sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients.

The ERG was concerned that the assumption that the benefits of tocilizumab continue over a lifetime regardless of the treatment duration did not appear to be justifiable based on early results from the OLE study and the published results from the previous RCT. The external evidence identified by the ERG also raised uncertainties regarding the external validity of the longer-term predictions from the economic model.

The ERG alternative base-case proposes alternative assumptions and data sources which we consider have greater face validity and are more consistent with the natural history of GCA reported in longer-term epidemiological studies. The ERG alternative base-case ICER results were higher than those reported by the company.

The ERG considers that the 1-year treatment period results provide the most internally valid estimates consistent with the treatment duration period assessed in the GiACTA trial. However, in the absence of a clear stopping rule for tocilizumab there remains significant uncertainty concerning the appropriate duration of tocilizumab treatment. The differences reported between the company and ERG highlight that important uncertainties remain concerning the optimal duration of tocilizumab treatment and the associated longer-term benefits

Although the 52-week tapering regimen is consistent with the most rapid tapering regimen recommended in the BSR/BHPR guidelines, there remains uncertainty surrounding the generalisability of this tapering regimen and the associated relapse rate to a longer tapering regimen (18-24 months) more conventionally used in clinical practice.

8.1 Implications for research

Further reliable research is needed to determine the effectiveness of tocilizumab in maintaining remission in patients with GCA in the long term.

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10 Appendices

Appendix Table 1 Time to Remission for subjects not in Remission at Baseline, ITT Population

PBO QW + 26 Week GC Taper (n=50)		PBO QW + 52 Week GC Taper (n=51)		TCZ QW + 26 Week GC Taper (n=100)		TCZ Q2W + 26 Week GC Taper (n=49)	
Patient	Time to remission (days)	Patient	Time to remission (days)	Patient	Time to remission (days)	Patient	Time to remission (days)
A1	28	B1	15	C1	22	D1	29
A2	86	B2	28	C2	8	D2	57
A3	8	B3	197	C3	22	D3	8
A4	23	B4	22	C4	8	D4	8
A5	8	B5	15	C5	9	D5	57
A6	9	B6	29	C6	8	D6	-
A7	8	B7	8	C7	-	D7	61
A8	8	B8	29	C8	8	D8	17
A9	107	B9	15	C9	15	D9	8
A10	8	B10	85	C10	9	D10	59
A11	8	B11	9	C11	30	D11	309
A12	-	B12	8	C12	11	D12	316
A13	8	B13	141	C13	8	D13	169
A14	8	B14	8	C14	8	D14	22
A15	-	B15	57	C15	-	D15	22
A16	85	B16	58	C16	8	D16	-
A17	8	B17	-	C17	33	D17	22
A18	7	B18	113	C18	8	D18	8
		B19	169	C19	8	D19	15
		B20	8	C20	8	D20	85
		B21	56	C21	8		
		B22	15	C22	86		
		B23	22	C23	8		
		B24	84	C24	8		
		B25	15	C25	8		
				C26	8		
				C27	9		
				C28	57		
				C29	142		
				C30	8		
				C31	6		
				C32	8		
				C33	15		
				C34	8		
				C35	6		
				C36	15		
				C37	7		
				C38	8		
				C39	8		
				C40	9		
				C41	29		
				C42	8		
				C43	12		
				C44	8		

Appendix Table 2 Number of patients who completed PROs at each time point

Patients completed PRO / patients completed blinded treatment	PBO QW + 26 Week GC Taper (n=50)	PBO QW + 52 Week GC Taper (n=51)	TCZ QW + 26 Week GC Taper (n=100)	TCZ Q2W + 26 Week GC Taper (n=49)
Baseline				
SF-36 PCS	48	49	97	49
SF-36 MCS	48	49	97	49
PGA VAS	49	51	100	49
FACIT-Fatigue	50	49	99	49
EQ-5D	50	49	99	49
Week 12				
SF-36 PCS	49	51	97	49
SF-36 MCS	49	51	97	49
PGA VAS	49	51	96	49
FACIT-Fatigue	-	-	-	-
EQ-5D	49	51	96	49
Week 24				
SF-36 PCS	46	46	90	46
SF-36 MCS	46	46	90	46
PGA VAS	47	47	90	46
FACIT-Fatigue	47	49	95	46
EQ-5D	47	47	91	46
Week 36				
SF-36 PCS	44	47	85	42
SF-36 MCS	44	47	85	42
PGA VAS	46	46	87	41
FACIT-Fatigue	-	-	-	-
EQ-5D	46	46	86	41
Week 48				
SF-36 PCS	43	45	82	40
SF-36 MCS	43	45	82	42
PGA VAS	44	46	84	41
FACIT-Fatigue	45	47	81	40
EQ-5D	44	45	84	40
Week 52				
SF-36 PCS	43	45	85	39
SF-36 MCS	43	45	85	39
PGA VAS	44	43	85	40
FACIT-Fatigue	44	45	84	40
EQ-5D	44	45	85	39

Appendix Table 3 Quality Checklist for Company Model

Company submission		Reviewer's judgment (Yes/No/Unclear/NA)	Notes
Study design			
1	Was the research question stated?	Yes	
2	Was the economic importance of the research question stated?	Yes	
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5	Were the alternatives being compared clearly described?	Yes	
6	Was the form of economic evaluation stated?	Yes	
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection			
8	Was/were the source(s) of effectiveness estimates used stated?	Yes	
9	Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of several effectiveness studies)?	NA	
11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12	Were the methods used to value health states and other benefits stated?	Yes.	
13	Were the details of the subjects from whom valuations were obtained given?	No	
14	Were productivity changes (if included) reported separately?	NA	
15	Was the relevance of productivity changes to the study question discussed?	No	
16	Were quantities of resources reported separately from their unit cost?	Yes	
17	Were the methods for the estimation of quantities and unit costs described?	No	
18	Were currency and price data recorded?	Yes	
19	Were details of price adjustments for inflation or currency conversion given?	No	
20	Were details of any model used given?	Yes	
21	Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	

Analysis and interpretation of the results			
22	Was time horizon of cost and benefits stated?	Yes	
23	Was the discount rate stated?	Yes	
24	Was the choice of rate justified?	Yes	
25	Was an explanation given if cost or benefits were not discounted?	NA	
26	Were the details of statistical test(s) and confidence intervals given forstochastic data?	No	
27	Was the approach to sensitivity analysis described?	Yes	
28	Was the choice of variables for sensitivity analysis justified?	No	
29	Were the ranges over which the parameters were varied stated?	Yes	
30	Were relevant alternatives compared? (i.e. Were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31	Was an incremental analysis reported?	Yes	
32	Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33	Was the answer to the study question given?	Yes	
34	Did conclusions follow from the data reported?	Yes	
35	Were conclusions accompanied by the appropriate caveats?	Yes	
36	Were generalizability issues addressed?	Yes	

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Tocilizumab for treating giant cell arteritis [ID1051]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 24 October 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12: Marketing authorisation date is now known.	Marketing authorisation granted 21st September 2017 (RoActemra is indicated for the treatment of Giant Cell Arteritis in adults).	Factual accuracy.	Corrected

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 & page 47: The ERG appear to have calculated HRs for subgroups for median time to disease flare for newly-diagnosed and relapsing patients. Although not included as part of the Company Submission, these data were provided in the CSR (page 118), with numbers slightly different to those calculated by the ERG (also 99% CI rather than 95% CI).	**ERG data**: New onset patients HR = 0.44, 95% CI 0.29 – 1.59; (p=0.004). Relapse patients HR = 0.33, 95% CI 0.14 - 0.81; (p=0.04) **CSR p118-119**: (no p-values given) New onset patients (HR = 0.44; 99% CI: 0.14 to 1.32) Relapse patients (HR = 0.36; 99% CI: 0.13 to 1.00)	Factual accuracy.	Corrected

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: The ERG refer on occasion to the study population in GiACTA and state that overall there was a higher ratio of large vessel GCA patients to cranial GCA patients than would be seen in NHS practice. This may be related to differences in diagnostic techniques rather than the	Roche agree that there may have been a higher proportion of patients with LVV in GiACTA than typically seen in UK general practice. However, this may be a consequence of imaging modalities used to diagnose rather than any differences in natural history of the disease in the UK. Suggest stating that since diagnostic techniques vary internationally the rates of LVV in the UK may be under estimated.	Diagnostic techniques routinely used in the UK may underestimate the rates of LVV.	Inserted sentence: 'However, this may be due to the difference in diagnostic techniques such as vascular imaging, which is more effective in diagnosing large vessel GCA patients. Therefore, the rates of LV GCA in the UK may be under estimated.'

aetiology of GCA.			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24-25: Figure 1: title is incorrect.	Figure 1: Pathway for management of GCA.	Correct the title for the treatment algorithm.	Corrected

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24: The ERG state that the BSR Guidelines GCA treatment pathway was not explained clearly, in terms of urgent referral for specialist management.	Within the Company Submission Roche reproduced the figure from the BSR Guidelines and believe that the algorithm clearly suggests urgent referral for specialist management once steroid treatment has been initiated in all patients.	To explain accurately the clinical utility of the BSR guideline.	Amended to clarify that the BSR guideline for the treatment pathway is slightly unclear rather than the company's explanation of it.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 79: The ERG report states 0.00025 is the probability of visual *loss* at	Suggest stating this is the rate of visual complications, rather than vision loss.	While this amendment will not impact the ICER calculations, Roche considers it to be a more	Not a factual inaccuracy. Although the Luqmani 2016 report refers to visual

relapse/flare, but the Luqmani 2016 HTA report this to be the rate of visual *complication*.		clinically appropriate representation of GCA complications, and accurate to the cited reference.	complications, the rates and associated costs and outcomes specifically relate to visual loss.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84: Prednisolone is described as being sold in 30 tablet packs, while it is sold in 28 tablet packs.	Suggest amending to read "prednisolone: £0.81 for 28 tablets at 5 mg each".	To our understanding the correct number has been applied in the economic modelling so may be a typing error only.	Corrected. This was a typing error and the correct number has been applied in the economic model.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100: The ERG state that "In the absence of robust evidence supporting a continuing effect of tocilizumab beyond the treatment period, the ERG considers that it is more appropriate to set the treatment duration benefit post-continuation to 0, such that the longer term QALY benefits of tocilizumab treatment are more closely related to the differences	Roche agree that there is a lack of robust evidence to quantify the continued effect of tocilizumab beyond 12 months. However, there are data sources that suggest the benefits of tocilizumab may be continued once treatment has stopped: • Evans et al (2016) 8 patient case series showing 3/8 were able to stop tocilizumab; all others continued on tocilizumab on a reduced dose with some able to also reduce frequency of infusions • Although Part 2 data presented in the	These data highlight the possibility of continued benefit to patients from tocilizumab after treatment has finished.	Not a factual inaccuracy. The ERG's alternative base-case allows for continued benefit but assumes that the differences between strategies in the post-discontinuation period arise from continuing prognostic differences due to the different distribution of patients in initial and subsequent remission health states

predicted during treatment duration period itself. " Roche believe there is possible continued treatment benefit, but recognise the lack of robust evidence to know with certainty the duration of that benefit.	company submission from GiACTA are incomplete, there is evidence to show that patients are able to remain in sustained remission beyond the first month after treatment discontinuation • The Villiger supporting study follow-up data show that 55% of tocilizumab patients relapsed with median time to relapse of 12.5 months (range 2-14), ie 45% had not relapsed after the last study infusion (Adler et al 2016). Suggest stating that modelling 0 months treatment benefit is a conservative approach, and the duration of benefit may be longer.		

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105: The modelled relapse rate has been amended according to a published observational study, but the design of that study is not as robust as GiACTA so flare events may not have been fully captured.	The ERG amended the relapse rate modelled from the GiACTA trial with data published from the Labarca et al 2016 study. Roche recognises Labarca 2016 as a good quality retrospective, observational study in GCA patients, and also the limited availability and inconsistent data published in this area. However, the limitations of the Labarca et al study design should be considered. Suggest stating that as a retrospective, observational study it is possible that relapse/flare events were not captured	Fully capture the limitations of the ERG basecase approach.	Not a factual inaccuracy. The ERG identified significant uncertainties and concerns regarding the characterisation of the longer-term natural history of GCA based on only the 52-week follow-up of the GiACTA study. The ERG does not consider that the observational nature of this evidence is a limitation in this context and the definitions of relapse appear in line with

	systematically, so these could be underreported, and subject to bias.		those reported in GiACTA.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typing errors: **<u>Page 14</u>**: Some of the Part 2 data should be marked as AIC.	The GiACTA trial has an ongoing Part 2, which is an open-label extension including patients from Part 1 who will be followed for an additional 2 years. Preliminary results from Part 2 were that 33% of TOCILIZUMAB QW+26 responders flared after discontinuation of tocilizumab, indicating that for a sustained treatment benefit, continued treatment with tocilizumab is needed in a substantial proportion of patients. Therefore, further reliable and accurate research is needed to determine the long term effectiveness of tocilizumab in maintaining remission in patients with GCA.	Factual accuracy.	Corrected. Note: as of 3/11/2017 the company no longer consider this data to be confidential.
<u>Page 54</u>: In the summary of the cost-effectiveness SLR, it is stated that 5 articles were screened in full, instead of 3 articles	Suggest amending the sentence to read "The remaining 3 studies were assessed in full."		Not a factual inaccuracy. The company submission states that a total of 316 articles were identified (314 from the electronic searches and 2 from supplementary searches). 311 of these 316 articles were stated to have been excluded at the primary screening stage, leaving 5 articles which were

			assessed in full.
Page 57: The adverse events row of Table 6 gives incorrect pages numbers within the main submission for Sections B.3.3.5. & B.3.3.6.	Sections B.3.3.5. & B.3.3.6 within the main submission document cover pages 106-108.		Not a factual inaccuracy. The submission also covers relevant discussion of tocilizumab related AEs on page 109.
Page 57: Utility decrements were only applied to GCA-related complications, while it was stated GC-related complications were also associated with utility decrements.	Amend sentence to state only GCA-related complications were associated with a utility decrement		Not a factual inaccuracy. The model does incorporate GC-related disutilities as discussed on p 82 of the ERG report.
Page 59: The word 'service' appears in the abbreviations of Table 6, which appears to have no connection with the table	Amend the Table 6 abbreviations footnote		Corrected.
Page 59: Amend the spelling of Kaplan-Meier	Amend the spelling of Kaplan-Meier		Corrected.

References

Adler S, Reichenbach S, Kuchen S, Wermelinger F, Dan D, Seitz M, Villiger PM. 2016. "Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT (ClinicalTrials.gov registration number: NCT01450137)." In.: Arthritis Rheumatol.

Evans, J., Steel, L., Borg, F., Dasgupta, B. 2016. ‘Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis’, RMD Open, 11;2(1):e000137.

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

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1 Summary

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

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

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

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

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

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

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

Sustained remission

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

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

Flare

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

Cumulative dose of GC

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

Sub-group analyses

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

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

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

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

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

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

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

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

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

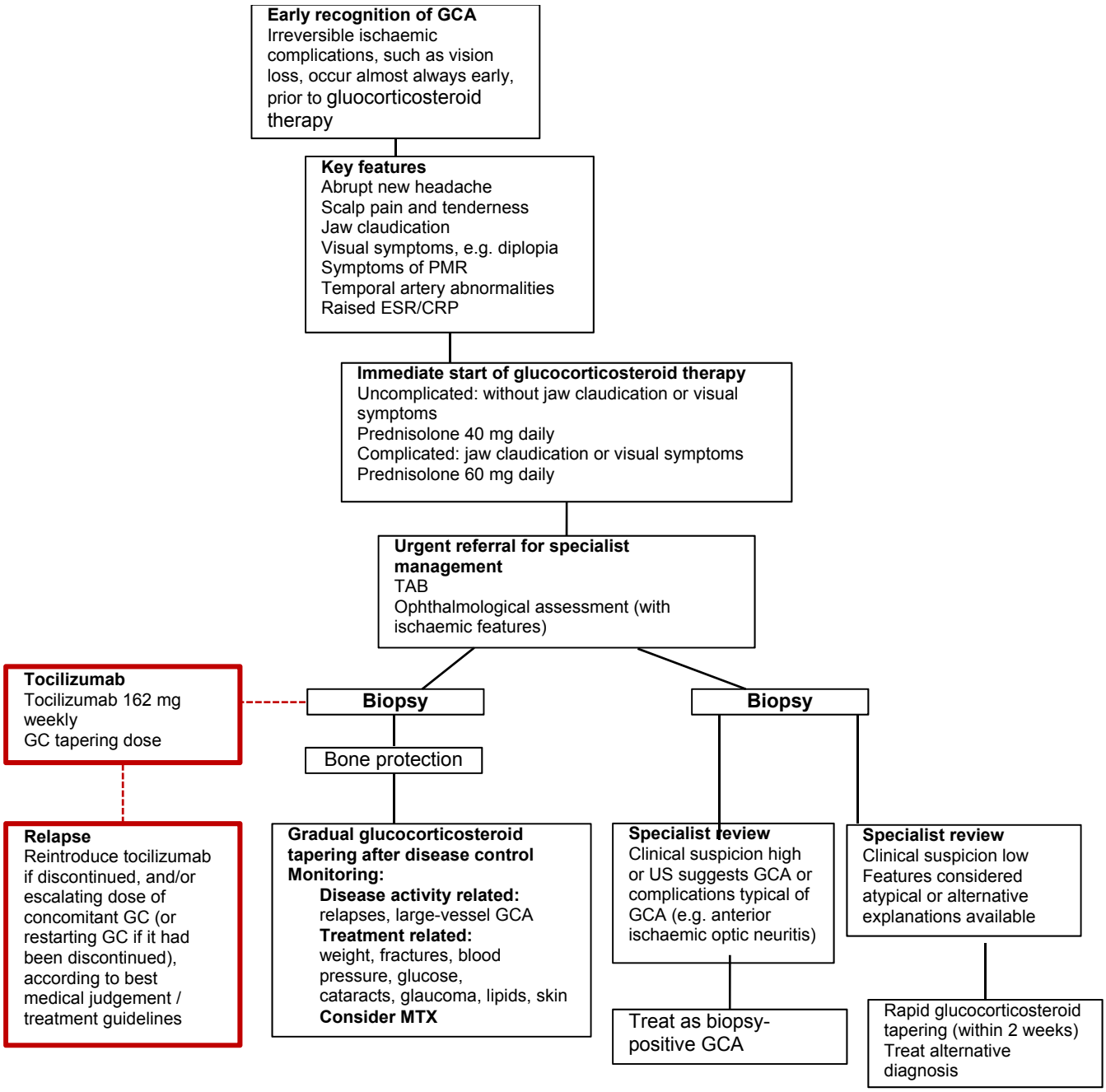
1.4 Summary of cost effectiveness submitted evidence by the company

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

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

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

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



3 Critique of company's definition of decision problem

3.1 Population

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

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

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

3.2 Intervention

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

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

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

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

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

3.2.1 Summary of results of GiACTA

Disease Remission

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

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

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

Cumulative GC dose by disease status at baseline (new-onset or relapsing) is presented in the CS Section E1.4. The NHS relevant arms are given in Table 1 below.

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

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

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

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

3.2.2 Model structure

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

The model structure is shown in **Error! Reference source not found.Error! Reference source not found.** and includes seven separate health states:

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

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

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

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

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

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

3.2.3 Resources and costs

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

The acquisition and monitoring costs of treating GCA patients with either TCZ-QW or prednisone alone are summarised in Table 2.

Table 2: Acquisition, administration and monitoring cost assumptions

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

Replicated from company submission

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

6.1 Overview

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

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

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

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

The probabilistic results are reported in Table 3, **Error! Reference source not found.** and **Error! Reference source not found.** for the ITT population, newly diagnosed and relapsed/refractory subgroups.

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

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

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