Public observer slides – no confidential information

Lead team presentation
Tocilizumab for treating giant cell arteritis [ID1051] – STA

1st Appraisal Committee meeting

Committee C

Clinical effectiveness

Lead team: Kamal Balakrishnan and Judith Wardle

ERG: CRD and CHE, University of York

NICE technical team: Ross Dent and Alex Filby

9 November 2017

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?

Disease background

- Giant cell arteritis causes inflammation in the walls of arteries, in the head and neck (cranial GCA) and less commonly the aorta (large vessel GCA)
- It is more common in people older than 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 and reduce risk of complications such as vision loss, stroke and aneurysm
- Initial treatment is with high-dose corticosteroids, such as prednisolone which is gradually reduced – ‘tapered’ – over a period of 18 to 24 months

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

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
- Tocilizumab treats the underlying cause of inflammation, rather than masking symptoms
- People who are intolerant of steroids will especially benefit

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

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. There are no age restrictions.
Administration and dose	• 162 mg subcutaneous injection once per week in combination with a tapering course of glucocorticoids • Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice (as stated in Summary of Product Characteristics) • Monotherapy should not be used to treat acute relapses
Cost	• List price: £913.12 for 4 syringes containing 162 mg tocilizumab • 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. There is no NICE guidance.

Clinical pathway of care

All patients suspected of having GCA have steroid treatment:

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

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

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

If patient relapses or 'flares':

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

Proposed benefits of tocilizumab:

- Reduce cumulative steroid dose and related adverse events through:

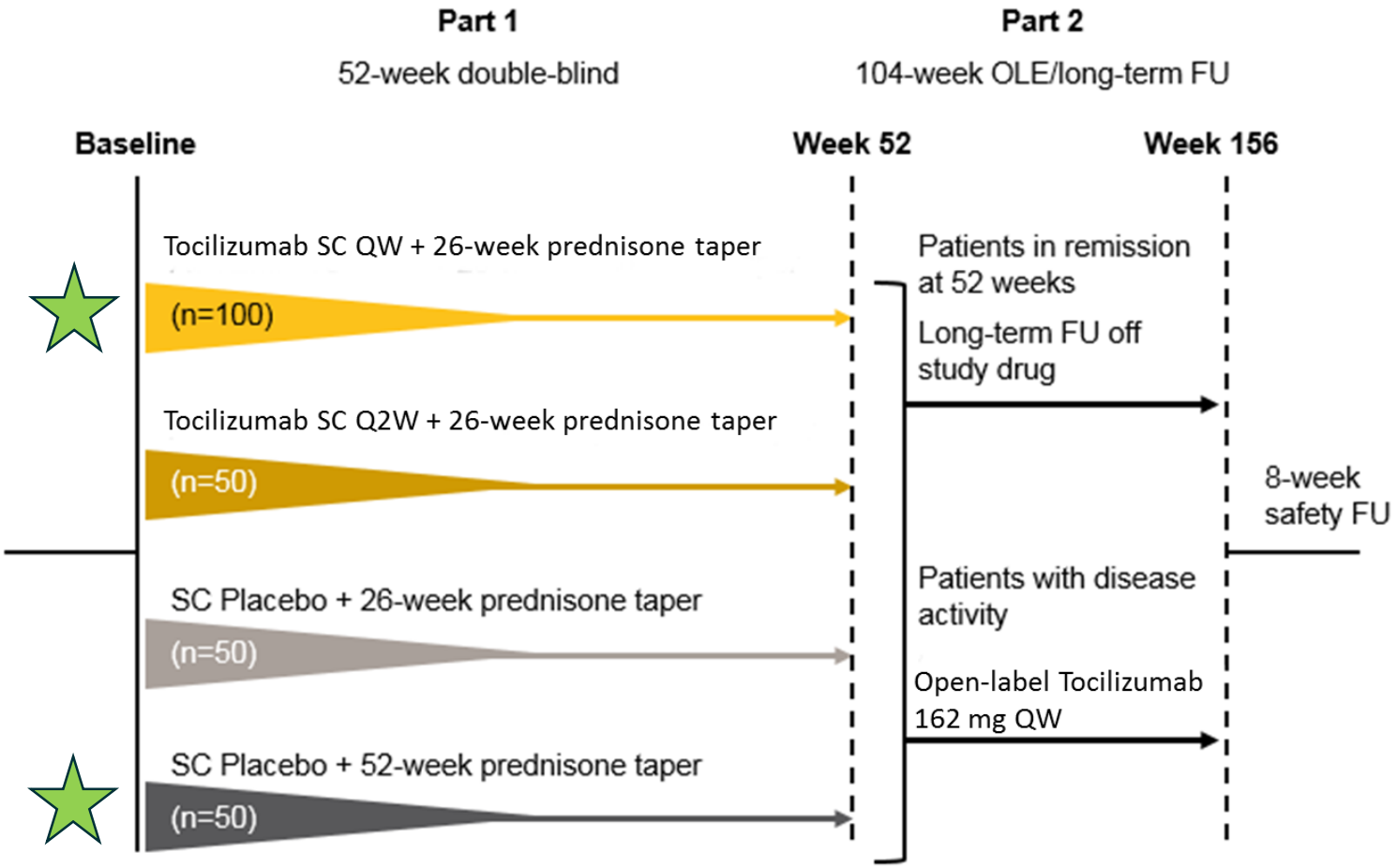
1) shorter tapering regimen and 2) lower relapse rate/longer remission reducing need for high steroid doses

Trial evidence – GiACTA trial

Description	• Phase III, multicentre, double-blind, placebo-controlled study • 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 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: dose must remain stable and not increase. 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

Population, comparator and outcomes in the trial and company's decision problem match the NICE scope

GiACTA trial design



QW, once a week; Q2W, once every 2 weeks; SC, subcutaneous; FU, follow-up

= used in economic model

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

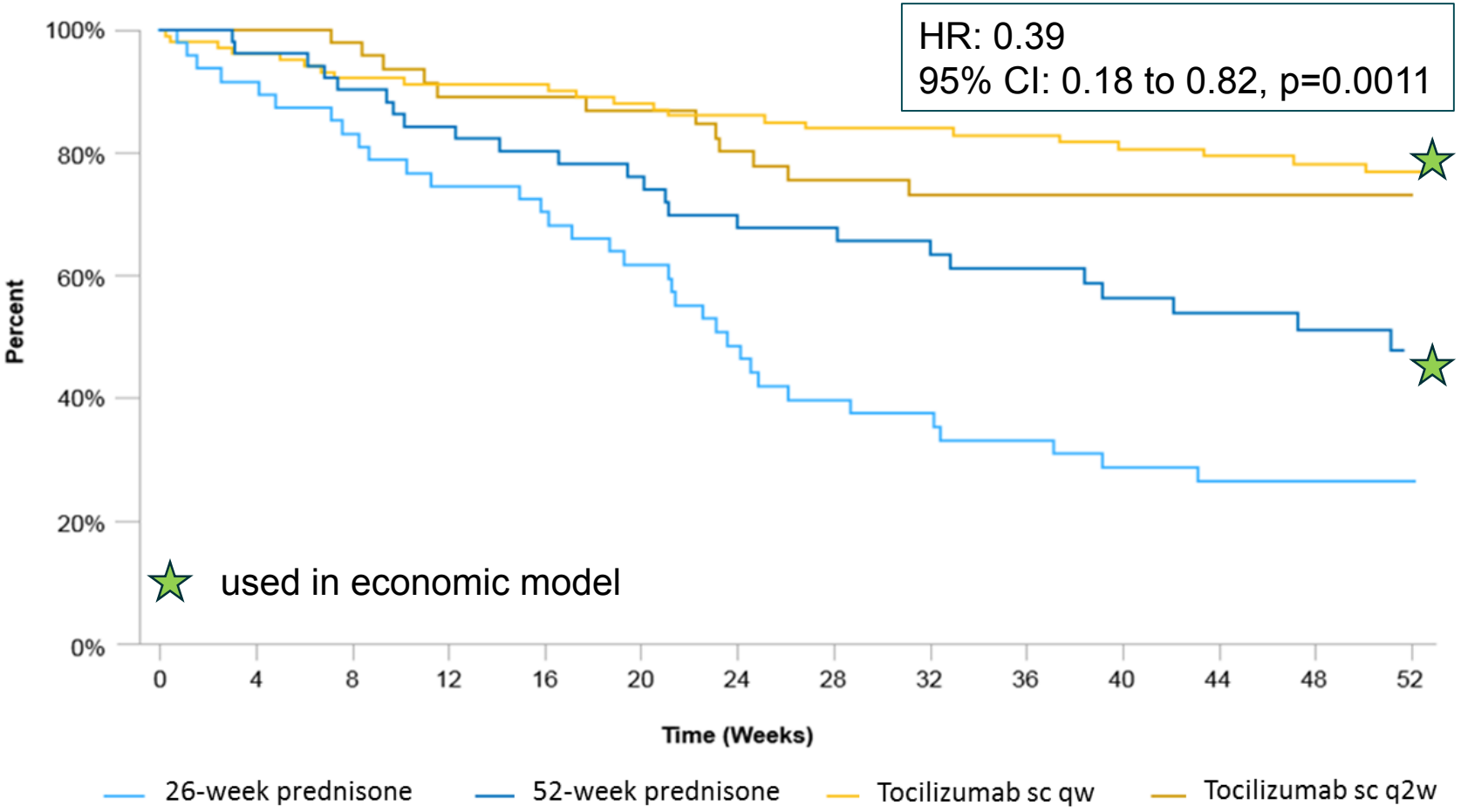
ERG comments on trial

- 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%)

GiACTA trial results – overall population

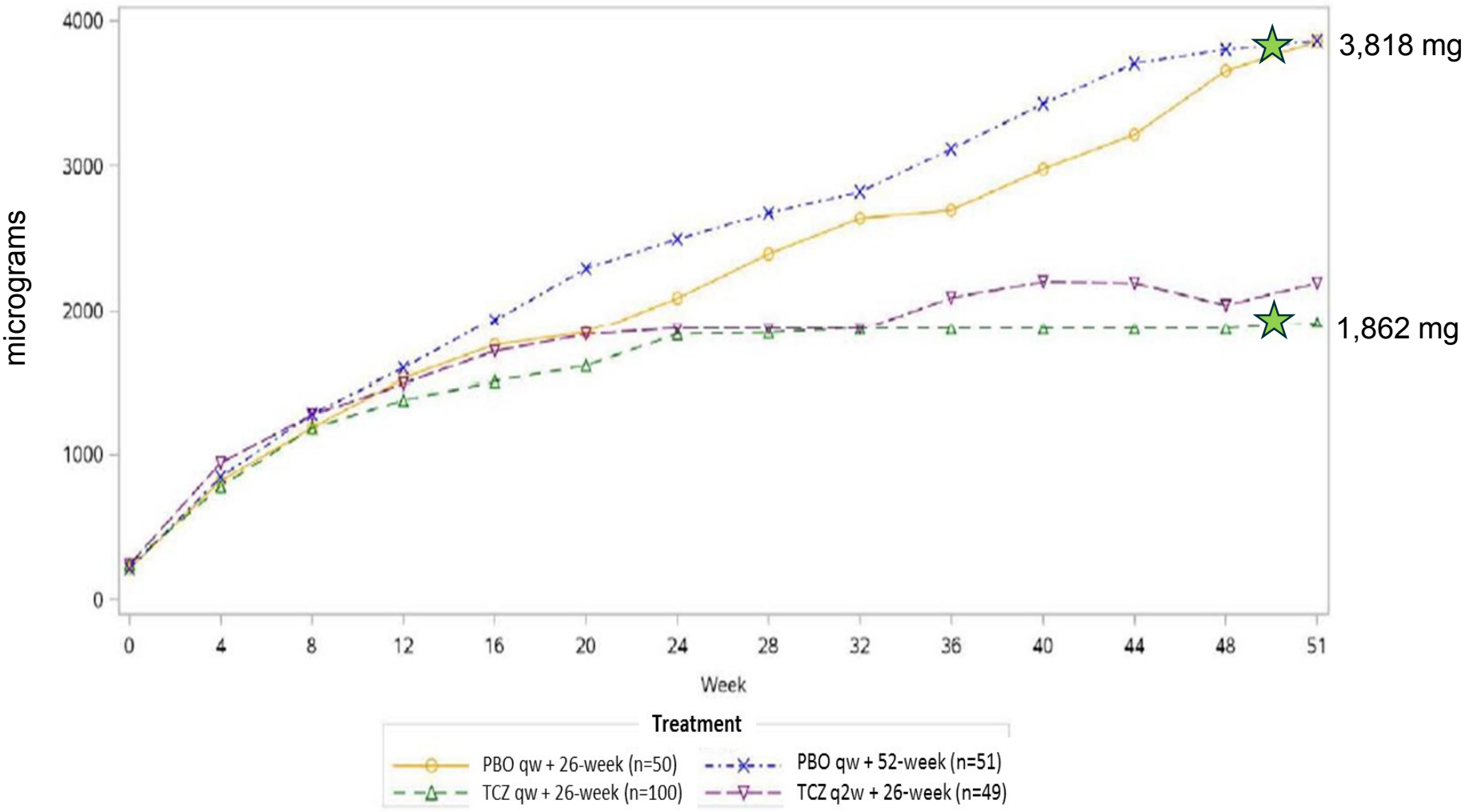
	Tocilizumab (weekly) + 26 week steroid taper n=100	Placebo + 52 week steroid taper n=51
Sustained remission at week 52	56.0%	17.6%
Unadjusted difference (99.5% confidence interval)	38.4% (17.89 to 58.81), p<0.0001	
Flare by week 52	23%	49%
Time to first flare: median	Not evaluable	295 days
Time to first 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	

Time to first flare – overall 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

Median cumulative steroid dose



★ used in economic model

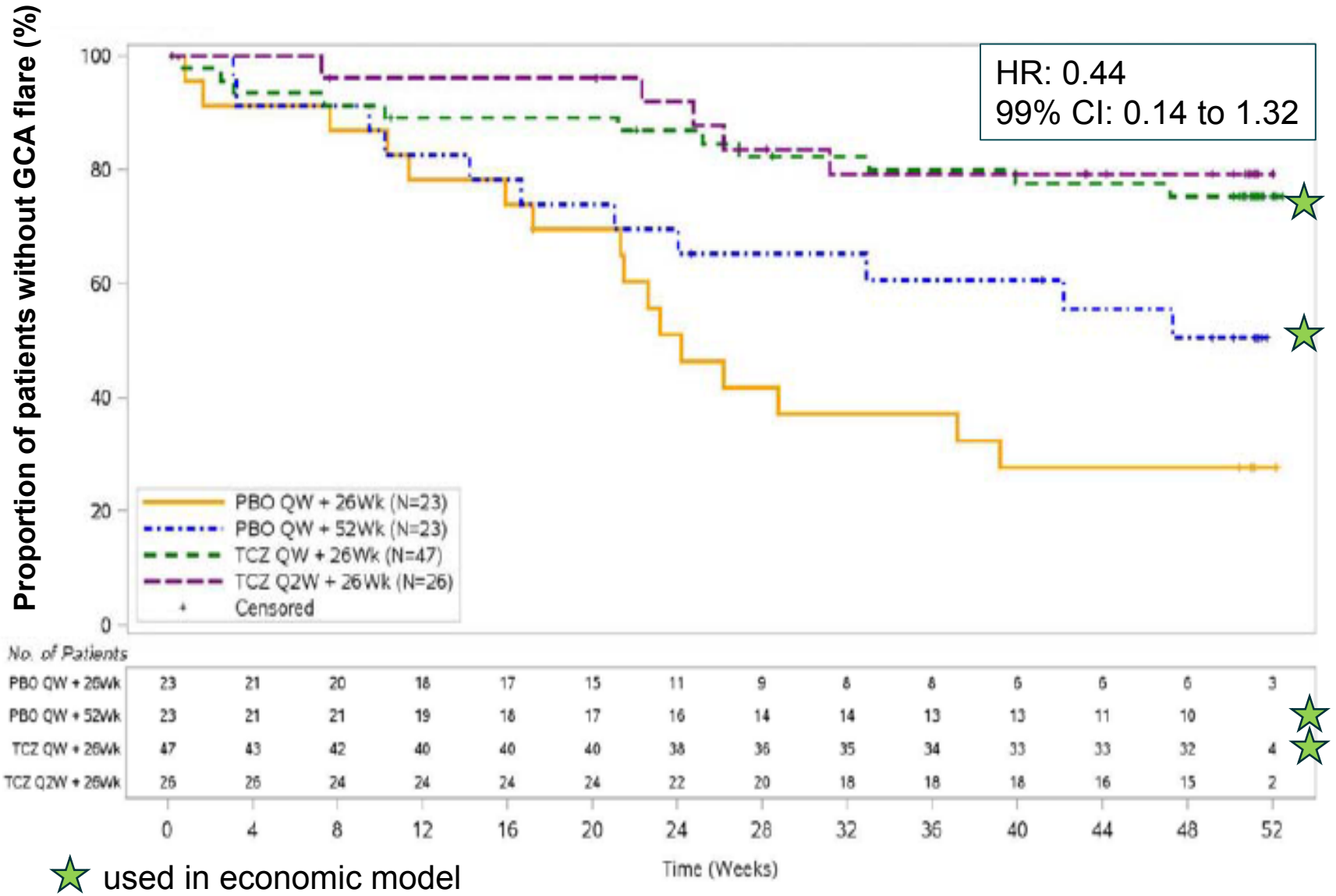
GiACTA trial results – subgroups

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)

Time to first flare – newly diagnosed



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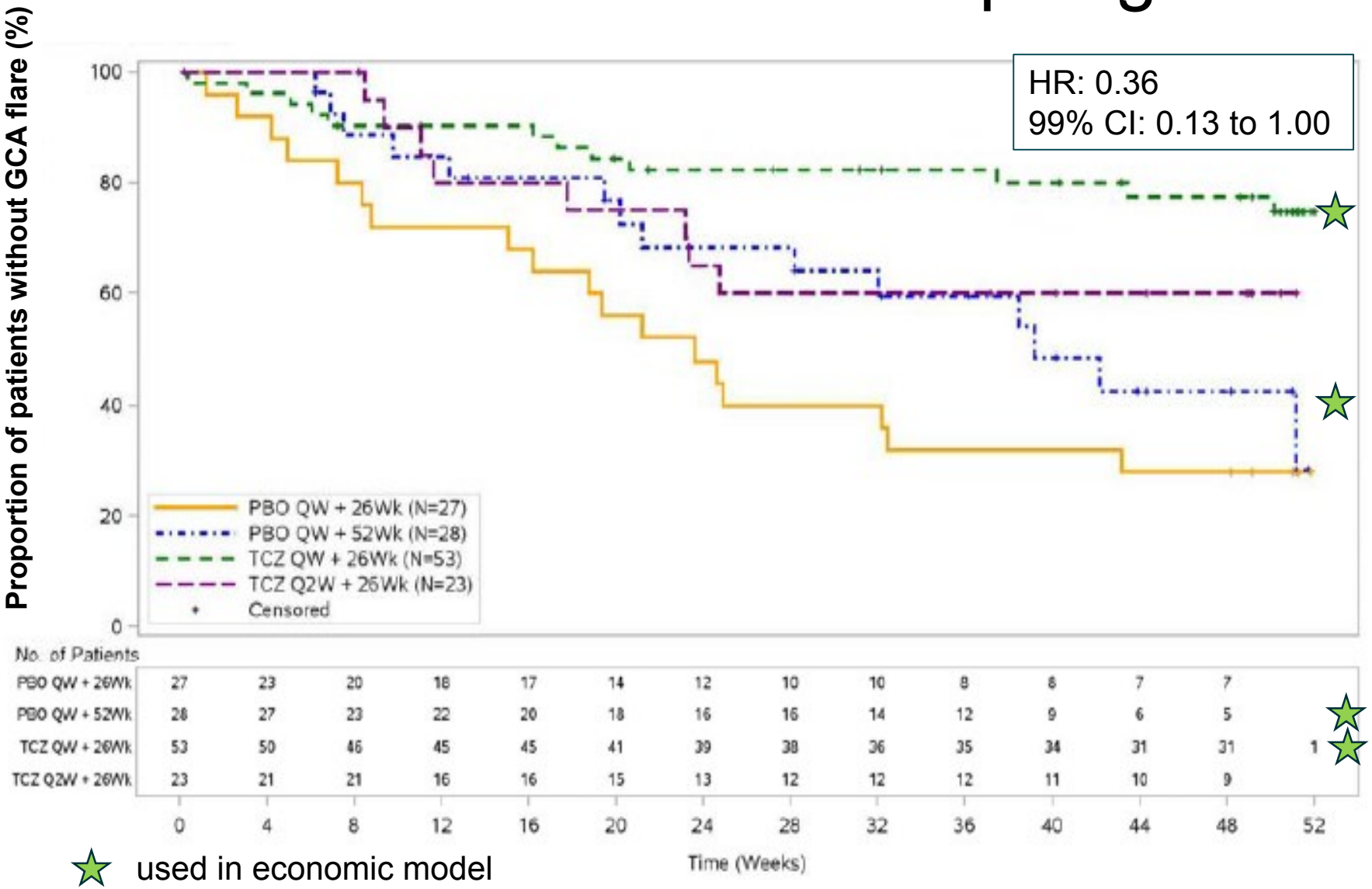
Time to first flare - relapsing



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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)
  - 
  - 
- **Treatment duration:** Clinical experts- no guidelines or evidence about when tocilizumab treatment should stop, 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

ERG comments on trial results

- Analysis for overall population did not take into account the difference between newly diagnosed and relapsing patients, nor between those that were in remission at baseline and those that were not
  - randomisation was stratified by baseline steroid dose which will account for some of the differences but not all
- Newly diagnosed and relapsing patient baseline characteristics and results suggest that these are 2 subgroups that require different treatment pathways
- 52 week steroid taper is the minimum recommended by BSR guidelines, but in clinical practice the average length is around 2 years
  - studies show that the initial steroid dose and tapering schedule influence the relapse rate
  - therefore uncertain how generalisable tapering regimen and relapse rate is to longer tapering regimen achieved in clinical practice
- Part 2 results suggest a sustained treatment benefit for a significant proportion of patients but continued treatment is required for many

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%

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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Cost effectiveness

Lead team: Peter Selby

ERG: CRD and CHE, University of York

NICE technical team: Ross Dent and Alex Filby

9 November 2017

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

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?

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

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:

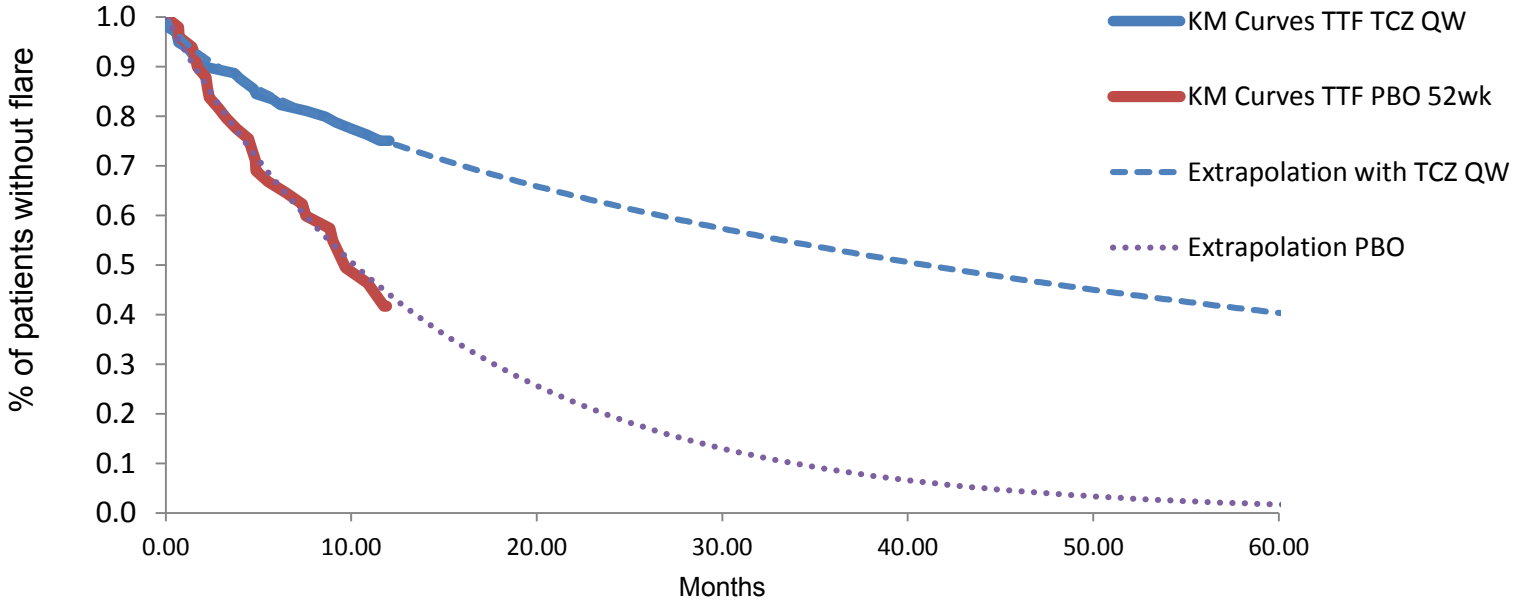
- Additional acquisition costs of tocilizumab
- More flares in prednisolone group, each flare has a cost attached
- Weekly management costs on steroids higher than off steroids, tocilizumab group spends less time on steroids

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%

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)



ERG critique of time to first flare extrapolation

- Different parametric models for each arm justified by statistical fit, but AIC values did not indicate large differences between distributions and other distributions had a better fit to the subgroup data
- Extrapolation predicts only 2% of patients in the prednisolone group will not have had a relapse by year 5 but longitudinal cohort studies suggest around 30-50% will not
- These studies also suggest the hazard of relapse decreases over time
- Risk of relapse highest during taper period, so long term trend after 52 weeks likely to be different to that observed during taper period
- Benefits of tocilizumab over placebo assumed to continue over a lifetime regardless of tocilizumab treatment duration
  - company rationale: in GiACTA part 2, few relapse after stopping tocilizumab, but ERG notes around 50% relapsed
  - another small study shows 55% stopping tocilizumab at 52 weeks relapsed (median time 5 months)

Transition: remission to subsequent flare

- Probability of subsequent flares estimated from GiACTA and assumed constant as flares can occur many years after diagnosis

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 not clinically logical for tocilizumab – higher for newly diagnosed population than relapsing population
- Total mean number of flares predicted for prednisolone overall population is 19.67 over 30 years which lacks external validity:
  - Proven reports a maximum of 7 flares in any single patient over median follow-up of 10 years - company model predicts mean of 10.35 over 10 years
  - Labarca reports median relapse rate equivalent to 2 relapses over 5 years - company model predicts 5.26 over 5 years

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

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

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

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			

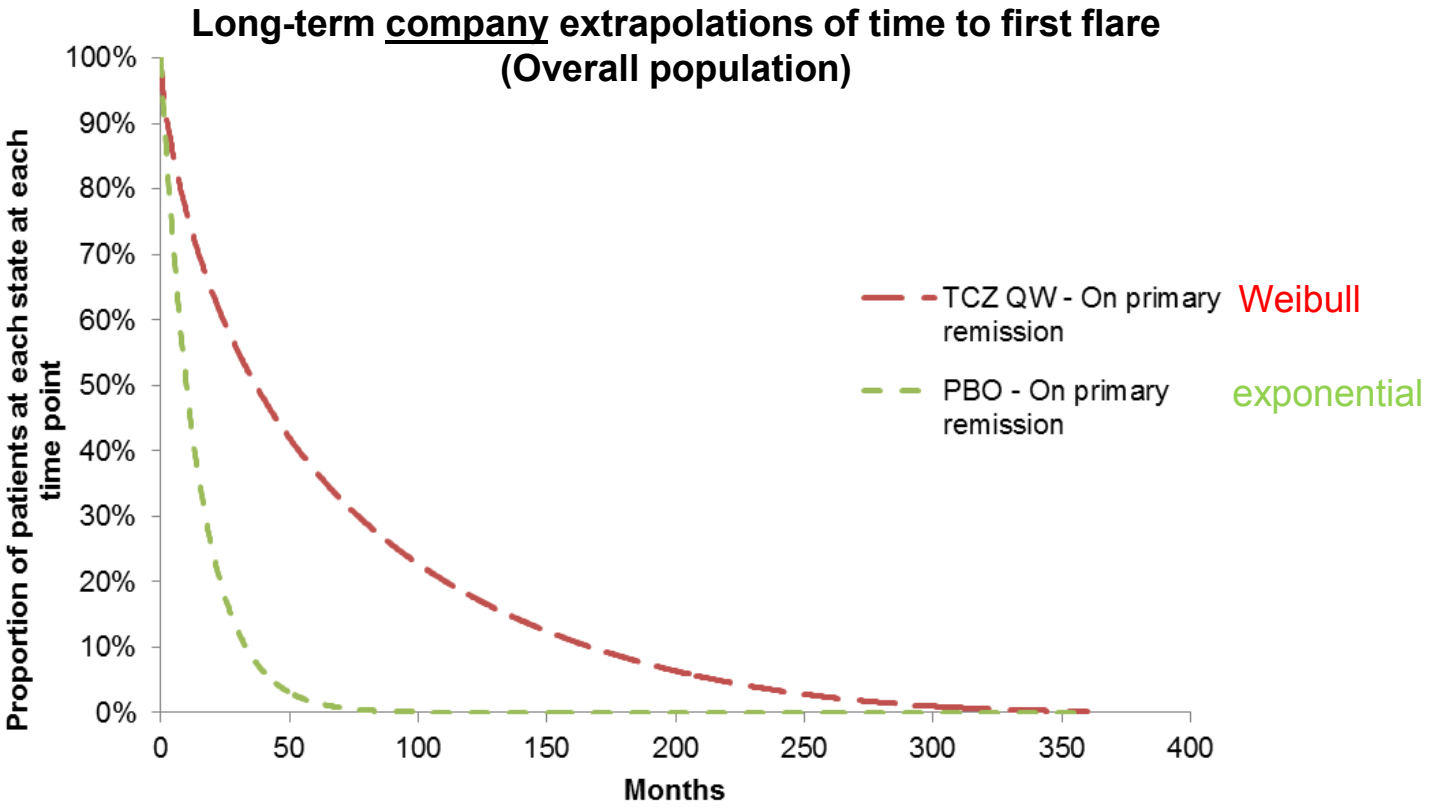
Company scenario analyses

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*

*ERG calculated

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



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

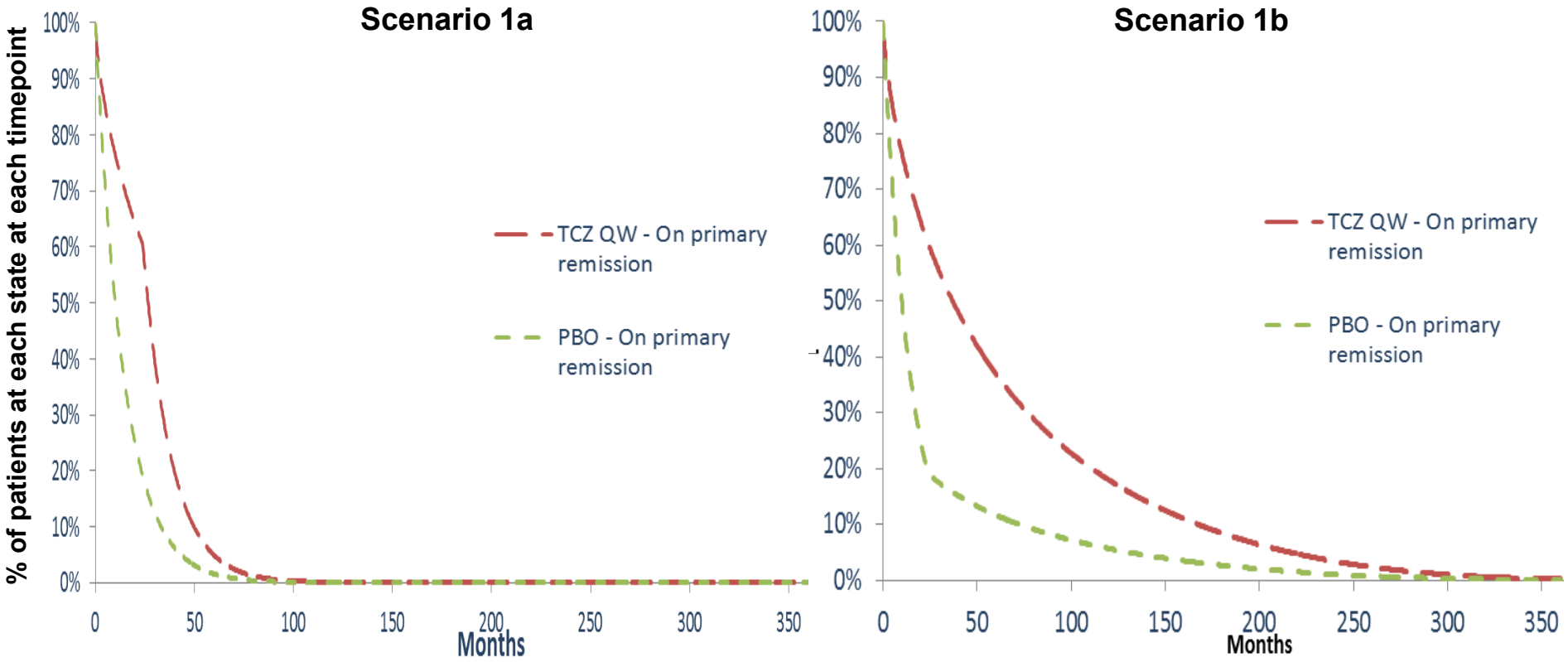
Scenario 1a

- 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)

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

ERG alternative modelling: subsequent relapses

- Company probabilities of subsequent relapses are clinically illogical for tocilizumab subgroups and lead to implausibly high estimates of flares
- ERG notes that Labarca estimate of 0.4 relapses/year may be a more plausible estimate for the prednisolone alone newly diagnosed subgroup
- ERG derives rates for other subgroups and for tocilizumab leading 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

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

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**

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

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

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

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?