# Upadacitinib for treating giant cell arteritis [ID6299]

Slide for presentation – contains no confidential information

**Technology appraisal committee D [10 December 2025]**

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**Company:** AbbVie

# ID6299: Upadacitinib for treating giant cell arteritis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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# Background on giant cell arteritis

- Chronic condition causing inflammation in medium to large arterial walls
- Commonly head and neck (cranial GCA) or less commonly aorta (large vessel GCA)
- Leads to narrowed arteries and restricted blood flow
- Cause unknown (possibly linked to genetics, infection or previous CVD)

**Epidemiology**

- Affects 2.2 per 10,000 in the UK, 2-3 times more common in women than men
- Around 1 in every 4,500 people aged 40 years and over develop giant cell arteritis each year in the UK
- Rare in people under 50, risk increases with age
- Relapsing in around 50% people

**Diagnosis**

- Usually confirmed with biopsy and ultrasound

**Symptoms and prognosis**

- Headache (most common), forehead tenderness, visual disturbances, jaw pain, fatigue, loss of appetite, fever

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Abbreviations: GCA; giant cell arteritis, CVD; cardiovascular disease

# Patient perspectives

GCA is a rare condition with limited treatment options

**Polymyalgia Rheumatica & Giant Cell Arteritis UK; Vasculitis UK**

- Living with GCA is difficult; it is an unpredictable condition with relapses, flares and remissions
- People often rely on carers especially in an acute phase
- Potential risk of vision loss/organ damage adds to increased anxiety
- Main treatment method is steroids
    - Control condition well, but serious side effects at high doses
- Alternative treatments like tocilizumab are not readily available or applicable in all cases
- Access to a wider choice of treatments is key to reducing:
    - Impact of long-term steroid use on individuals
    - Cost to NHS in treating/managing steroid-related side effects

Living with this condition is often described as a "living nightmare“

“It’s all so very difficult to cope with at times. I’m not the person I was”

[After tocilizumab treatment] “very fearful about having it removed after 12 months and not being able to have it again if they relapse in future”

Abbreviations: GCA; giant cell arteritis

# Clinical perspectives

Large unmet need for more steroid-sparing treatment options

**The British Society for Rheumatology**

- Main aim of treatment with upadacitinib: induce sustained remission for people with relapsing-remitting disease or at high risk of steroid-related side effects
- First line treatment is steroids, tapered over 12-18 months
    - Relapse rates can be 50-80%
    - Relapsing disease: clinicians consider methotrexate (off label) or tocilizumab (TA518)
- Currently only one other steroid-sparing treatment (tocilizumab); limited to 12 months use
    - Data suggests only approximately 50% response rate with tocilizumab
- Upadacitinib is already used for other rheumatological conditions, so most centres will already have adequate training, specialist nurse support and experience with this drug
- If commissioning follows TA518 with implementation via specialised centre approval, this would disadvantage patients living in remote and rural locations

# Equality considerations

Equality issues related to disease prevalence and access to treatment

**Patient and professional groups highlighted:**

- Older people are disproportionately affected by GCA, which almost exclusively affects adults over the age of 50 years, with increasing incidence with each subsequent decade
- It more commonly occurs in women than men (2-3 times greater incidence)
- Current treatment tocilizumab is prescribed in specialist centres
    - Older people living in rural areas, frailer people or people with disabilities may face challenges accessing specialised centres
    - People on lower incomes may be disproportionately affected by having to travel further distances to access treatment

Are all relevant equality issues considered?



Abbreviations: GCA; giant cell arteritis

# Upadacitinib (RINVOQ, AbbVie)

| | |
|---|---|
| **Marketing authorisation** | • Indicated for the treatment of giant cell arteritis in adult patients |
| **Mechanism of action** | • Upadacitinib is a selective and reversible inhibitor of the Janus associated tyrosine kinase JAK1.<br>• This reduces signalling in certain pathways involved in inflammation including interleukin-6 (IL-6) and interferon- γ (IFN-γ), associated with GCA |
| **Administration** | • 15mg oral tablet taken once daily in combination with tapering course of corticosteroids<br>• Upadacitinib can be continued as monotherapy* following discontinuation of corticosteroids<br>• Treatment beyond 52 weeks permitted |
| **Special warnings and precautions for use** | Upadacitinib should only be used if no suitable treatment alternatives are available in patients: 65 years of age and older; patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); patients with malignancy risk factors (e.g. current malignancy or history of malignancy) |
| **Price** | • List price £806.56 (28 x 15mg tablets)<br>• Confidential patient access scheme applicable |

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* Upadacitinib monotherapy should not be used for acute relapses

Abbreviations: GCA; giant cell arteritis

# Key issues

| Issue | ICER impact |
|---|---|
| **Comparators & clinical effectiveness** | |
| Exclusion of tocilizumab as a comparator and lack of ITC | Unknown |
| New onset subgroup: modelling of treatment sequencing | Unknown |
| Trial data limited to 1 year | Unknown |
| **Cost effectiveness** | |
| 2- year stopping rule | Large |
| New onset subgroup: Choice of extrapolation for modelling time to flare | Large |
| Reliability of GCA flares modelling | Unknown |
| Modelling of steroid related conditions | Unknown |
| Frequency of rheumatology clinic visits | Moderate |
| Different modelling assumptions | Large |



Abbreviations: GCA; giant cell arteritis, ITC; indirect treatment comparison

# Treatment pathway

**New onset disease**

**High dose corticosteroids if no vision loss; Severe cases with acute visual symptoms:**
- IV methylprednisolone daily for 3 days
- Followed by oral corticosteroid therapy

**Disease remission**

**Corticosteroids:** Tapered gradually to ≤5 mg/day over 12-24 months

**Relapsing disease**

**Corticosteroids**
- Minor relapse: increase to last effective dose
- Major relapse: increase to 40-60mg daily

**+ Tocilizumab [TA518]*** Weekly (SC) alongside corticosteroid tapering, up to one year

**+ Immunosuppressants (off label, inconsistent use)** e.g. methotrexate*

Company propose upadacitinib + corticosteroid tapering for all adults with GCA

Company provide results for overall population & include subgroup results split by:
- new onset
- relapsed disease

**NHSE:** Tocilizumab commissioning via specialised centre approval. Likely upadacitinib to have similar commissioning arrangements

How would upadacitinib be used in clinical practice?



* Tocilizumab and methotrexate not included by company as comparators [key issue ]

# Key issues: Comparators in relapsed disease subgroup

Company submission excludes tocilizumab & methotrexate

**Background:**

- Tocilizumab (recommended for R/R GCA in TA518; comparator was tapering course of corticosteroid) and methotrexate listed as comparators in final NICE scope for relapsed disease

**Company:**

- Tocilizumab not included by company due to 1-year maximum treatment duration & company's clinical experts highlighted limited use. Excluded methotrexate as not routinely used due to uncertainty in its effectiveness

**EAG comments:**

- EAG's preliminary adjusted ITC suggested possibility of difference in clinical effectiveness between tocilizumab and upadacitinib. Agree appropriate to exclude methotrexate.

**Other considerations**

- Patient and professional organisations highlight unmet need for alternative treatments especially for GCA patients with previous glucocorticoid toxicity who have not relapsed or in relapsed patients not suitable for tocilizumab or those previously given tocilizumab
- Upadacitinib should only be considered if no suitable alternative treatment available in over 65 and with other risk factors (marketing authorisation special warning and precaution for use)

Are tocilizumab and methotrexate considered relevant comparators in relapsed disease?

Abbreviations: R/R; relapsing refractory, GCA, giant cell arteritis; ITC, indirect treatment comparison.

# Key issue: Treatment sequencing in new onset subgroup

## Should sequencing of treatment options for new onset group be considered?

### Background

- If tocilizumab and/or methotrexate are a relevant comparator (see issue) the new-disease onset subgroup becomes relevant as treatment pathway is potentially split based on comparators
- For the new onset subgroup: company compares upadacitinib + 26-week steroid tapering vs placebo + 52-week steroid tapering without allowing patients in the placebo arm to switch to tocilizumab or upadacitinib upon relapse

### Company

- Modelling of treatment sequencing without robust IPD and comparative effectiveness risks producing misleading ICERs
- Relapsing cohort already captures the post-flare experience for patients who progress on steroids alone.

### EAG comments

- Company has data for new onset subgroup including time to first flare (TTFF) and time to second flare (TTSF)
- EAG expert advice approx. 40% new onset patients successful taper and not flare again.

- Is the new onset subgroup relevant?
- How are treatments sequenced for patients in clinical practice at first / subsequent relapse?
- Should treatment sequencing be explored in the cost effectiveness modelling?

Abbreviations: IPD; individual patient data, ICER; incremental cost effectiveness ratio, TTFF; time to first flare, TTSF; time to subsequent flare

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# Key clinical trial – SELECT-GCA

## Clinical trial designs and outcomes

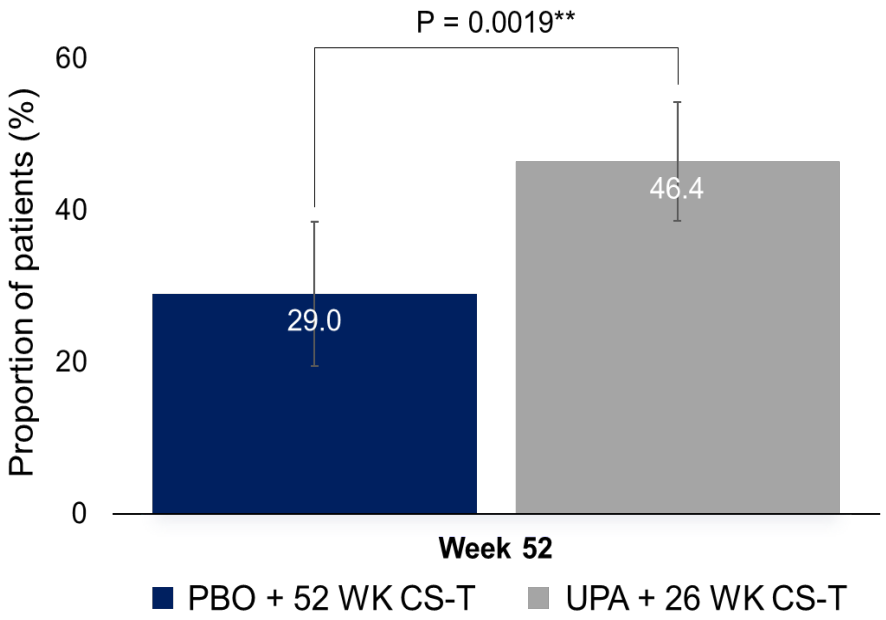
| | |
|---|---|
| **Design** | Phase 3 randomised, double blind, placebo controlled, multicentre trial |
| **Phases** | Period 1: safety and efficacy of upadacitinib up to 52 weeks<br>Period 2: 52-week blinded extension for patients on upadacitinib in remission |
| **Population (ITT)** | Adults aged 50 and above with active GCA (either new onset or relapsing) |
| **Subgroups** | New onset and relapsing GCA |
| **Intervention** | Upadacitinib (15mg once daily) with a 26 week CS taper regimen |
| **Comparator** | Placebo with a 52-week CS taper regimen |
| **Duration** | 104 weeks (period 1 - 52 weeks) |
| **Primary outcome** | Proportion with sustained remission at 52 weeks |
| **Key secondary outcomes** | Proportion with sustained complete remission from week 12 to week 52<br>Time to first GCA flare, proportion with at least one GCA flareup to week 52, cumulative CS exposure, adverse events, HRQoL |
| **Locations** | 100 sites in 23 countries (including 10 UK sites) |
| **Used in model?** | Only data from period 1 |

Abbreviations: GCA; giant cell arteritis, CS; corticosteroid; ITT, intention to treat

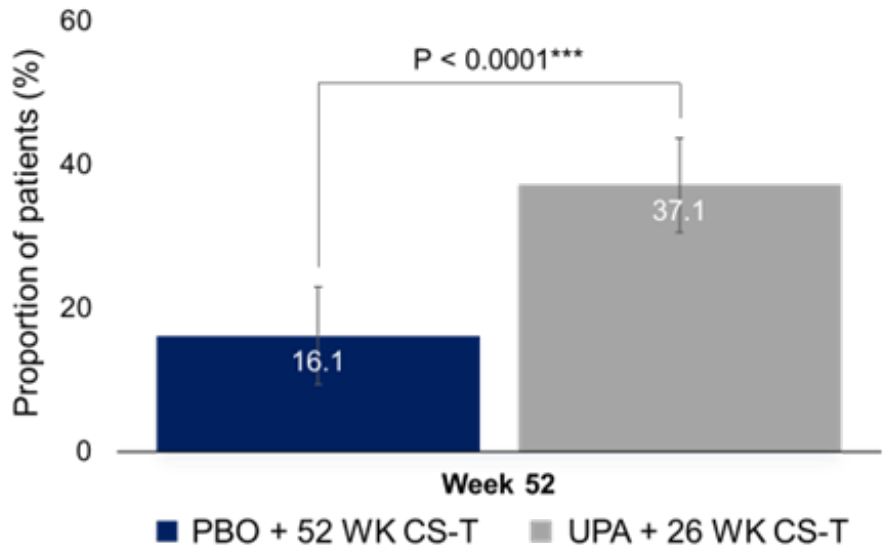
# Key clinical trial results – SELECT-GCA

Upadacitinib improves GCA disease control compared to corticosteroids

**Proportion achieving sustained remission week 12-52 (ITT population)**




**Proportion achieving sustained complete remission week 12-52 (ITT population)**




*supplementary appendix key clinical trial results

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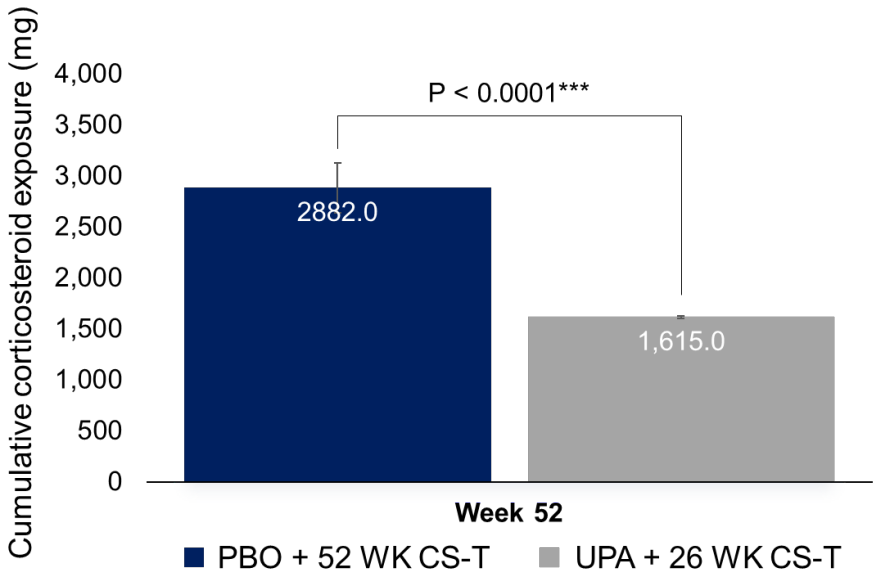
Abbreviations: GCA; giant cell arteritis, PBO; placebo, UPA; Upadacitinib, CI; confidence intervals

# Key clinical trial results – Cumulative corticosteroid exposure to week 52 (ITT population)

Statistically significant reduction in median cumulative corticosteroid exposure (prednisone/prednisolone equivalent) to week 52




| Measure | Upadacitinib 15 mg | Placebo | p-value |
|---|---|---|---|
| Median cumulative corticosteroid exposure (mg) through Week 52 | 1,615 mg (95% CI: 1,615, 1,635) | 2,882 mg (95% CI: 2,762, 3,253) | < 0.0001 |

Abbreviations: PBO; placebo, UPA; upadacitinib, CI; confidence interval

# Key clinical trial results – SELECT-GCA (subgroups)

## Upadacitinib improves GCA disease control compared to corticosteroids in new onset and relapsed disease subgroups

Company presents subgroup results for the new onset and relapsing disease subgroups showing improvement in proportion achieving sustained remission at week 52 for people with new onset and relapsing GCA

**Proportion achieving sustained remission week 12-52**

| GCA type | Upadacitinib 15mg | Placebo |
|---|---|---|
| New onset GCA | 48.1% | 32.2% |
| Relapsing GCA | 42.3% | 22.2% |

**Proportion achieving complete sustained remission week 12-52**

| GCA type | Upadacitinib 15mg | Placebo |
|---|---|---|
| New onset GCA | [redacted] | [redacted] |
| Relapsing GCA | [redacted] | [redacted] |

Only relevant if committee consider new onset and relapsed disease are appropriate subgroups to consider

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Abbreviations: GCA; giant cell arteritis

# Key issue: No clinical effectiveness data beyond 1 year

## Background

- Original CS did not include clinical effectiveness data beyond year 1 from pivotal trial SELECT-GCA

## Company

- Company provided period 2 data before ACM1 (included in committee papers)
- Period 2 cohort included patients who received upadacitinib during Period 1 (up to 52 weeks) and achieved remission for at least 24 weeks, then were re-randomised to either continue upadacitinib or switched to placebo
- Period 2 represents a distinct patient population from Period 1. Period 2 is not methodologically suitable for determining time to first flare across both periods and therefore should not be used to inform model extrapolations

## EAG comments

- Time to first flare data limited to year 1. Period 2 data would be useful to inform longer-term extrapolation of the key effectiveness outcome - Year 2 data time to flare data useful
- Even if year 2 trial data would be difficult to incorporate into modelling, could still be informative e.g. assessing resource use costs, adverse events etc.

Would period 2 data be useful to inform time to flare extrapolations?



Abbreviations: GCA; giant cell arteritis

Only relevant if committee consider tocilizumab a relevant comparator

# Key issue: EAG indirect treatment comparison (1/2)

## Background

- Company did not consider tocilizumab relevant comparator in relapsed subgroup. EAG performed indirect comparison for upadacitinib vs tocilizumab across the ITT, new onset and relapsed groups

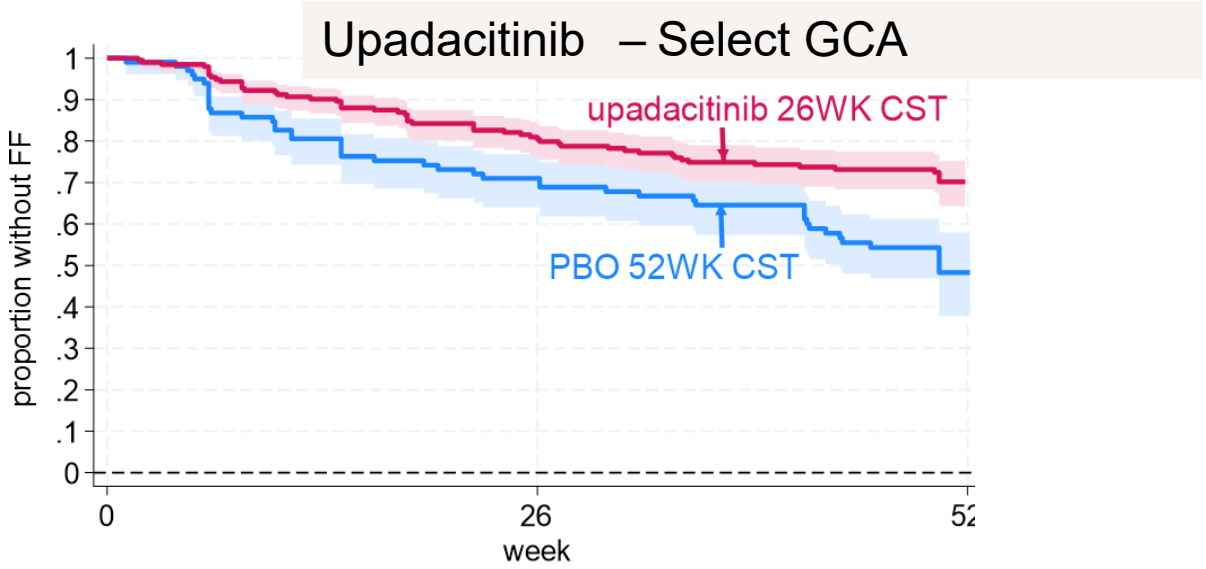
**Adjusted ITC based on risk ratios and hazard ratios indicated no significant difference between upadacitinib and tocilizumab; All results favour tocilizumab**

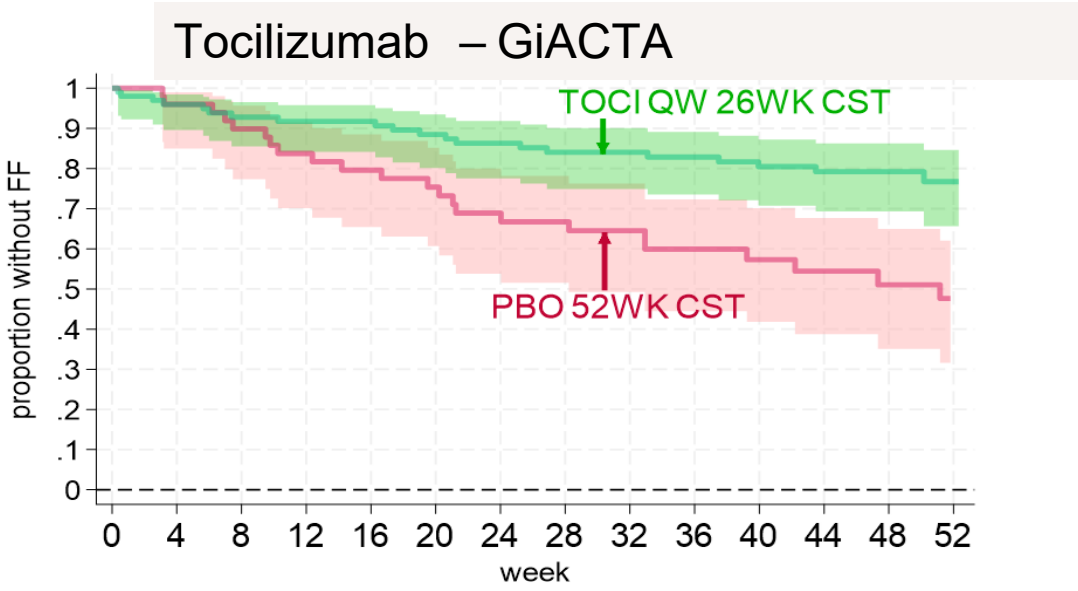
| RR (95% CI) | Upadacitinib vs Placebo (SELECT -GCA) ITT population | Tocilizumab vs placebo (GiACTA) | Adjusted indirect comparison |
|---|---|---|---|
| Population | Upadacitinib 15 mg daily vs placebo (52-week tapering) | Tocilizumab 162 mg weekly vs placebo (52-week tapering) | Upadacitinib vs tocilizumab |
| Sustained remission at week 52 (Risk ratio) | | | |
| ITT | 1.58 (1.14 to 2.17) | 3.17 (1.71 to 5.89) | 0.50 (0.25 to 1.00) |
| New onset | [redacted] | 2.74 (1.22 to 6.16) | [redacted] |
| Relapsing | [redacted] | 3.70 (1.44 to 9.49) | [redacted] |
| Experiencing at least 1 flare by week 52 (Risk ratio) | | | |
| ITT | 0.62 (0.48 to 0.80) | 0.47 (0.30 to 0.74) | 1.32 (0.79 to 2.22) |
| Time to first flare (hazard ratio)* | | | |
| New onset | [redacted] | 0.44 (0.14 to 1.32) | [redacted] |
| Relapsing | [redacted] | 0.36 (0.13 to 1.00) | [redacted] |

*There was uncertainty related to confidence intervals for the hazard ratios reported in TA518

# EAG indirect treatment comparison (2/2)

EAG compared KM plots for time to first flare (TTFF) at week 52 for ITT population in upadacitinib and tocilizumab trials




| Restricted mean survival estimates of TTFF | | | |
|---|---|---|---|
| ITT SELECT GCA | | | |
| | PBO 52wk CST | UPADAC 26wk CST | INTERVENTION-CONTROL |
| 51 wks | 37.08 (33.3 -40.8) | 42.3 (40.0 -44.6) | 5.23 (0.8 -9.6) |
| ITT GiACTA | | | |
| | PBO 52wk CST | QW TOCI 26wk CST | |
| 51 wks | 36.35 (31.1- 41.6) | 44.2 (41.3-47.2) | 7.88 (1. 9-13.9) |

**EAG:** Restricted mean survival estimates of TTFF KM plots show larger benefit with tocilizumab vs placebo: EAG consider difference between tocilizumab and upadacitinib is sufficiently large – inferiority of upadacitinib cannot be ruled out. More robust analysis helpful

Is upadacitinib clinically similar to tocilizumab? Should a more robust ITC be conducted?

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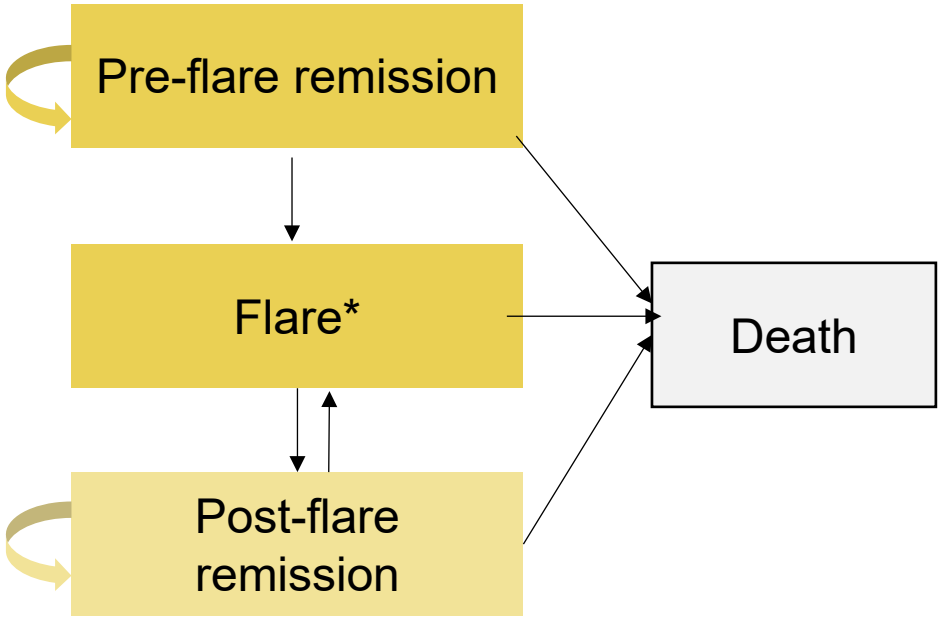
# Company's model overview

## Model structure (semi-Markov in line with TA518)




*Four tunnel states incorporated to enable modelling of GCA flare related complications

- **Intervention:** Upadacitinib with a 26-week steroid taper and a 2 year stopping rule
- **Comparator**: Placebo and a 52-week steroid taper.
- **Patient population:** ITT same mix of new onset and relapsing GCA patients as in the SELECT-GCA trial.
- **Subgroups**: results split by new onset & relapsing GCA

In the company model (ITT population) the main driver of the QALY gains are the conditions exacerbated by steroids.

How company incorporated evidence into the model and sources

Abbreviations: GCA; giant cell arteritis, ITT; intention to treat

# Key issue: Modelled treatment duration

## Background

- Company base case includes 2-year treatment duration
- Marketing authorisation does not include a stopping rule

## Company

- Does not consider the 2-year treatment duration a 'stopping rule'
- Treatment duration for GCA should be guided by disease activity, clinician judgement, and patient choice
- Stopping rule would prevent flexible treatments for patients and should be avoided
- Company explores other duration scenarios

## EAG comments

- The longer the treatment duration of upadacitinib the worse its cost effectiveness
- EAG revised base case ICERs for different stopping rules for the ITT population range from £35,371 per QALY at 1 year treatment duration to £150,612 per QALY for 5-year treatment duration

Should there be a stopping rule and if so what length should it be?

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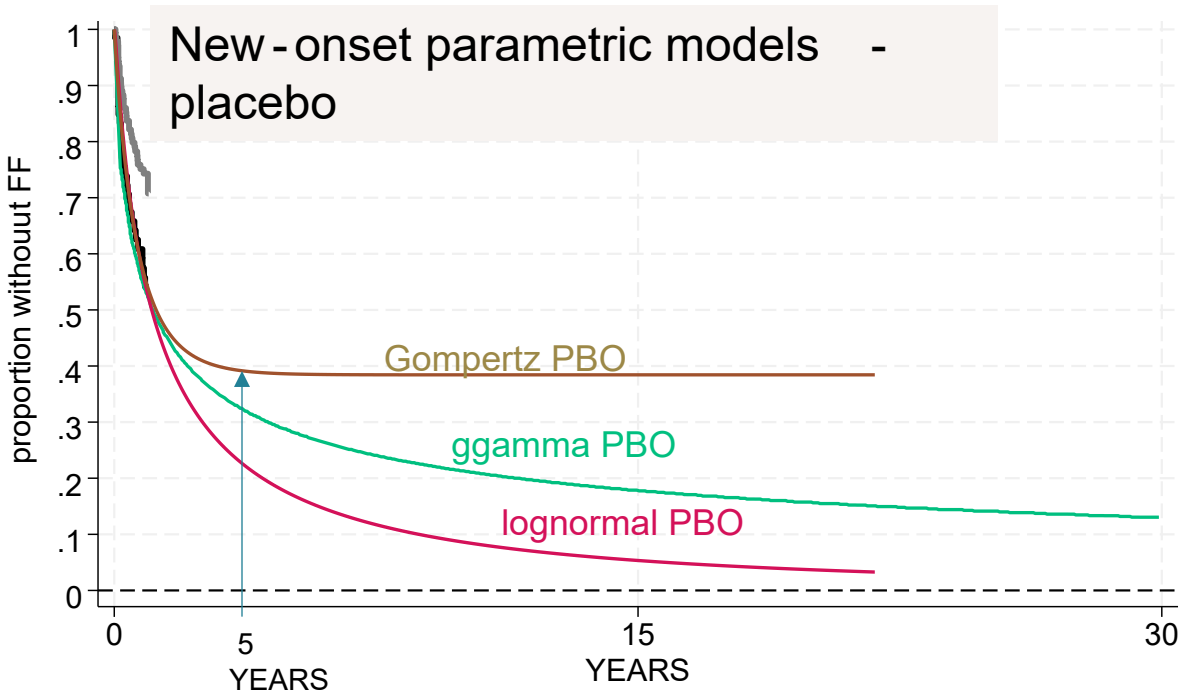
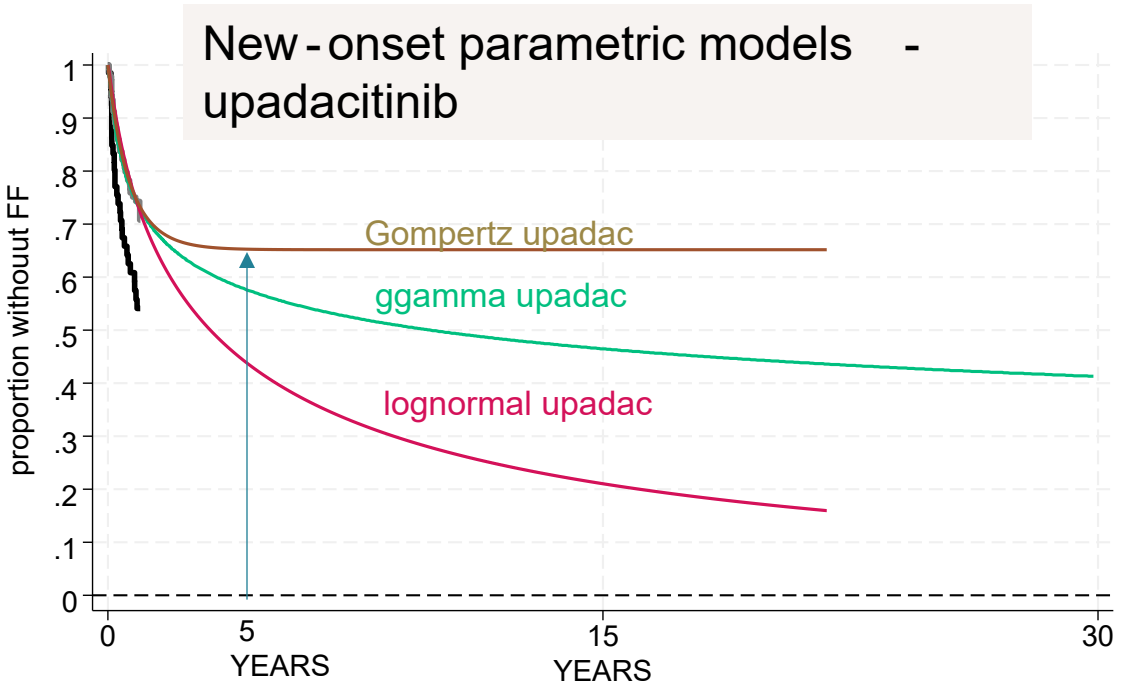
Abbreviations: GCA; giant cell arteritis, ICER; incremental cost effectiveness ratio, ITT; intention to treat, QALY; quality adjusted life year

# Key issue: Modelling time to first flare in new onset group (1/2)

Only relevant if committee consider new onset subgroup is appropriate to consider

Depending on parametric model selection; treatment effect is maintained indefinitely




**Company preferred Gompertz**: predicts no waning around 5 years for placebo and upadacitinib.

**EAG preferred Log-normal**: predicts ~27% in the placebo arm have not experienced FF at 3 years

Abbreviations: GCA; giant cell arteritis, FF; first flare

# Key issue: Modelling of time to first flare in new onset subgroup (2/2)

EAG says assuming no treatment waning is uncertain as disease modifying effect unlikely

**Company**

- Company base case for new onset subgroup selects Gompertz TTFF curves. Applies placebo probabilities of flare in the upadacitinib arm when treatment stops.

**EAG comments**

- Company Gompertz TTFF curves for upadacitinib and placebo have little to no probability of flare from year 5. Results in treatment effect maintained indefinitely
- EAG expert opinion is that it is questionable whether upadacitinib is disease modifying and once stopped it is likely that its anti-inflammatory effects will wane
- In TA518 expert opinion suggests Gompertz is too optimistic and log-normal too pessimistic when modelling the placebo arm at 3 to 5 years. At 10 years it suggests Gompertz is too optimistic and log-normal is about right.
- Short follow up and small number of participants in subgroup make it difficult to decide which of the available models can be used with confidence
- EAG uses log-normal in base case, explores generalised gamma and Gompertz in scenarios
- Provides exploratory treatment waning assumptions at 3,5,8,11 years from year 3 onwards

Which curve is appropriate for modelling time to first flare for upadacitinib and placebo in the new onset subgroup? Is it appropriate to consider treatment waning?

Abbreviations: TTFF; time to first flare

# Key issue: Modelling of GCA flare complications

## Uncertainty in company's modelling of GCA flare complication rates

**Background**

- The model inputs for the risks of complications related to GCA flares is either mainly related to rates at GCA diagnosis or just a general association with having GCA

**Company comments:**

- Company incorporates annual incidences of risks based on incidence at initial diagnosis

**EAG comments**

- EAG suggests some sources company uses to estimate incidences are estimates for GCA patients in general and not from those in flare
- EAG expert opinion is that rates of complications at presentation are somewhat higher than at subsequent flares due to diagnosing preexisting conditions
- EAG suggests data on rates of GCA flare complications from SELECT-GCA for relapsing patients could help improve accuracy of modelling for subsequent flares
- EAG provides an exploratory sensitivity analysis reducing the risk of stroke related complications by 50% and 25% of company base case. This has a moderate impact on the ICER

Are the risks estimated by the company for GCA flare related complications valid?

Abbreviations: GCA; giant cell arteritis, AE; adverse event, ICER; incremental cost effectiveness ratio

# Key issue: Modelling steroid related complications

Steroid related complications major driver of QALY gains; EAG has concerns with company approach

**Background:**

- Company uses real-world evidence source to determine risk of steroid related complications. Assumes risks of developing steroid complications is a function of the total cumulative steroid use from diagnosis.

**Company**

- Real-world evidence source preferred over SELECT-GCA rates because overall corticosteroid adverse event rates were low in trial likely due to long-term nature of events, short follow up and controlled environment.

**EAG comments**

- Concerns that evidence of steroid related complications is based on non-trial data with large difference in rates between 2 sources
- Uses incidence of steroid complications from 1st year diagnosis as proxy for annual risk: applies over model time horizon. EAG expert opinion suggests incidences higher in first year due to simultaneous identification of underlying conditions upon GCA diagnosis (e.g patient tested for osteoporosis)
- Provides exploratory scenarios; excluding the modelling of steroid related complications and a scenario assuming the increased risk from steroids for a subset of complications wanes and their risks are determined by steroid use in the previous year



Is the company's approach to modelling steroid related complications appropriate?

# Key issue: Frequency of rheumatology visits during tapering

## CS assumes monthly clinic visits based on TA518 estimates

### Background

- The company uses estimates from TA518; based upon a market survey
  - Suggests 0.9 visits per month to rheumatology outpatients when tapering steroids

### Company

- This approach taken as, due to controlled trial settings, HCRU in SELECT-GCA does not accurately reflect what is expected to be seen in clinical practice
- Model assumes 25.9% visit frequency distribution pre-flare remission on steroids and 24.5% post flare remission on steroids

### EAG comments

- Expert opinion: 75% of patients manage with fewer visits, the remainder being roughly equally split between those requiring slightly more visits and those requiring monthly visits (approx. 1 visit every other month or 0.45 visits per month)
- Suggests scenario analysis that halves the ongoing monitoring costs; this also halves the other elements of monitoring costs
- Further expert opinion on frequency of visits during initial steroid tapering and after tapering useful

Which estimates of frequency of rheumatology clinic visits are appropriate for decision making?

Abbreviations: GCA; giant cell arteritis, HCRU; health care resource use costs

# Key issue: Different modelling assumptions

**Background**

- EAG rebuilt company model and identified 7 assumptions which it considered errors and corrected - has a large impact on ICER
- Company consider they are EAG preferred assumptions and not errors

| EAG corrections with large impacts on costs and QALYs | Difference in costs | Difference in QALYs |
|---|---|---|
| Company base case | [redacted] | [redacted] |
| 2.Company: only those on steroids get new complications associated with steroid use. EAG: Patients off steroids remain at risk of developing complications from previous use. | [redacted] | [redacted] |
| 3. Company overestimated incidences of complications by not taking into account prevalence. For example model assumes that at 6.6 years when 83% of patients are alive all have osteoporosis. EAG corrects this. | [redacted] | [redacted] |
| 4. Company converts annual incidence rates of complications of flares into weekly probabilities but does not adjust eligible population after events occur, leading to an overestimation of total annual events. This has a large impact on higher incidence complications. | [redacted] | [redacted] |
| 5. Company retains 26-week steroid tapering in the upadacitinib arm after stopping at 2 years rather than switching to the 52-week taper modelled for placebo arm | [redacted] | [redacted] |

Model corrections 1,6&7 have minimal impacts on costs/QALYs



Are the EAG's model changes valid?

# Further issues identified by the EAG

| Issue | Company approach | EAG base case | Impact on ICER | Key question for committee |
|---|---|---|---|---|
| Age at baseline | 71.1 (SELECT-GCA) | 73 (TA518 preference for UK CPRD data) | Small | What is the most appropriate model starting age? |
| QoL Decrements | Transient conditions related to GCA flares and conditions exacerbated by steroid use are treated as QALY decrements | Implies durations of these conditions on QoL is 1 year. Clinical opinion is duration of some events <1 year, (see appendix for changes) | Moderate | Are the EAG estimates appropriate? |
| Event costs | Range of costs related to GCA flare & steroid use included. | EAG concerned costs are not appropriate - update several costing assumptions | Moderate | Are the updated costs from the EAG appropriate? |

Abbreviations: GCA; giant cell arteritis, CPRD; clinical practice research datalink, QoL; quality of life, QALY; quality adjusted life year

# Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

| Assumption | Company base case | EAG base case |
|---|---|---|
| **Baseline age** | 71.1 | 73 years |
| **Population** | ITT | ITT |
| **subgroups** | New onset GCA & Relapsed | New onset GCA & Relapsed |
| **Flare duration** | 4 weeks | 4 weeks |
| **Time to first flare extrapolation: new onset group** | Gompertz | Log normal |
| **Treatment duration** | 2 years | 2 years |

Further changes from EAG include updating minor issues, including minor stroke not having a permanent quality of life effect, MACE having a permanent quality of life effect, and applying a net probability for myocardial infarction.



Abbreviations: ITT; intention to treat, GCA; giant cell arteritis

# Cost-effectiveness results

# ITT Company base case and EAG corrected company base case

| Company base case | Total | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| Technologies | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs | ICER (£/QALY) |
| Upadacitinib | [redacted] | 10.634 | [redacted] | [redacted] | 0.053 | [redacted] | Dominant |
| Placebo | [redacted] | 10.581 | [redacted] | - | - | - | - |

| EAG corrected company base case | Total | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| Technologies | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs | ICER (£/QALY) |
| Upadacitinib | [redacted] | 10.634 | [redacted] | [redacted] | 0.053 | [redacted] | £38,359 |
| Placebo | [redacted] | 10.581 | [redacted] | - | - | - | - |

# Company and EAG base case vs placebo

| | ITT | | | New onset | Relapsed |
|---|---|---|---|---|---|
| | ICER | Inc costs | Inc QALYs | ICER | ICER |
| Company Base Case | Dominates* | [redacted] | [redacted] | Dominates* | Dominates* |
| EAG01: Model corrections | £38,359 | [redacted] | [redacted] | £4,614 | £70,797 |
| EAG02: Baseline age 73 years | £38,725 | [redacted] | [redacted] | £6,096 | £69,414 |
| EAG03: Log-normal time to first flare | .. | [redacted] | [redacted] | £23,344 | .. |
| EAG04: Transient QoL durations | £46,147 | [redacted] | [redacted] | £5,415 | £86,560 |
| EAG05: Event costs | £44,129 | [redacted] | [redacted] | £8,138 | £78,787 |
| EAG06: Minor issues | £41,206 | [redacted] | [redacted] | £6,192 | £70,576 |
| **EAG base case: EAG01-EAG06** | **£57,558** | [redacted] | [redacted] | **£42,918** | **£98,754** |
| **EAG probabilistic base case** | **£64,876** | .. | .. | **£46,598** | **£115,042** |

*** Upadacitinib dominates placebo**

- Main QALY gain in company model is from less steroid related disutility [redacted]QALY). In EAG model its[redacted]QALYs
- Main cost-offset in company base case is from less steroid related AEs (~£[redacted]). In EAG base case its <£[redacted]

NICE Abbreviations: ITT; intention to treat, QOL; quality of life

# ID6299: Upadacitinib for treating giant cell arteritis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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# Other considerations

## Uncaptured benefits

**Company:**

- In an elderly population, the short half-life of upadacitinib is potentially advantageous when there is a requirement to stop treatment quickly in the occurrence of opportunistic infections
- Patient preference for oral treatment

Are there any benefits that have not been captured in the modelling?

## Managed access

- Company did not submit a managed access proposal

# ID6299: Upadacitinib for treating giant cell arteritis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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# Key issues

| Issue | ICER impact |
|---|---|
| **Comparators & clinical effectiveness** | |
| Exclusion of tocilizumab as a comparator and lack of ITC | Unknown |
| New onset subgroup: modelling of treatment sequencing | Unknown |
| Trial data limited to 1 year | Unknown |
| **Cost effectiveness** | |
| 2- year stopping rule | Large |
| New onset subgroup: Choice of extrapolation for modelling time to flare | Large |
| Reliability of GCA flares modelling | Unknown |
| Modelling of steroid related conditions | Unknown |
| Frequency of rheumatology clinic visits | Moderate |
| Different modelling assumptions | Large |



Abbreviations: GCA; giant cell arteritis, ITC; indirect treatment comparison

# ID6299: Upadacitinib for treating giant cell arteritis

# Supplementary appendix

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# Decision problem

Population, intervention, comparators and outcomes from the scope

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Population** | • Adults with giant cell arteritis | • As per NICE scope | • SELECT-GCA trial population slightly younger but broadly similar to the eligible population |
| **Intervention** | • Upadacitinib | • As per NICE scope | • NICE scope and CS both in line with marketing authorisation for upadacitinib |
| **Comparators** | • Tapering course of steroids<br>• Tocilizumab<br>• Methotrexate (off license) | • Tapering course of steroids<br>• Consider tocilizumab not relevant as restricted to one year treatment duration and low use in clinical practise | • EAG consider exclusion of tocilizumab as a key omission<br>• (See key issue 1)<br>• EAG agree with exclusion of methotrexate |
| **Outcomes** | • Disease remission, time to relapse, cumulative dose, adverse events, HRQoL | As per NICE scope | N/A |

Abbreviations: GCA; giant cell arteritis, CS; company submission, HRQoL; health related quality of life

# SELECT-GCA baseline characteristics

Baseline characteristics for intervention and comparator

| Characteristic | Upadacitinib (n=209) | Placebo (n=112) |
|---|---|---|
| Age (mean) | 70.8 | 71.6 |
| Sex | Female n=156  Male n=53 | Female n=77 Male n=35 |
| Race group | White n= 199 Non white n= 10 Hispanic or Latino n=6 not Hispanic or Latino n=203 | White n=103 Non-white n=9 Hispanic or Latino n=5 not Hispanic or Latino n=107 |
| Nicotine use | Current =32<br>Former =63<br>Never = 11<br>Unknown =3 | Current =13<br>Former =33<br>Never = 66<br>Unknown = 0 |
| Weight (mean, kg) | 68.99 | 71.13 |
| BMI (mean) | 25.80 | 25.27 |

Are these baseline characteristics generalisable to NHS clinical practice?

Abbreviations: GCA; giant cell arteritis

Return to results

# Key clinical trial results – SELECT-GCA

Greater proportion of subjects achieving sustained remission week 12-52 compared with placebo

| Outcome | | Placebo + 52 WK CS-T | UPA + 26 WK CS-T |
|---|---|---|---|
| n | | 112 | 209 |
| Sustained remission | n (%) | 33 (29) | 97 (46.4) |
| | 95% CI† | 20.6, 37.5 | 39.6, 53.2 |
| Response rate difference compared to placebo | Diff (%) | | 17.4 |
| | Adj. Diff (%) | | 17.1 |
| | 95% CI‡ | | 6.3, 27.8 |
| | **P-value** | | **0.0019**** |

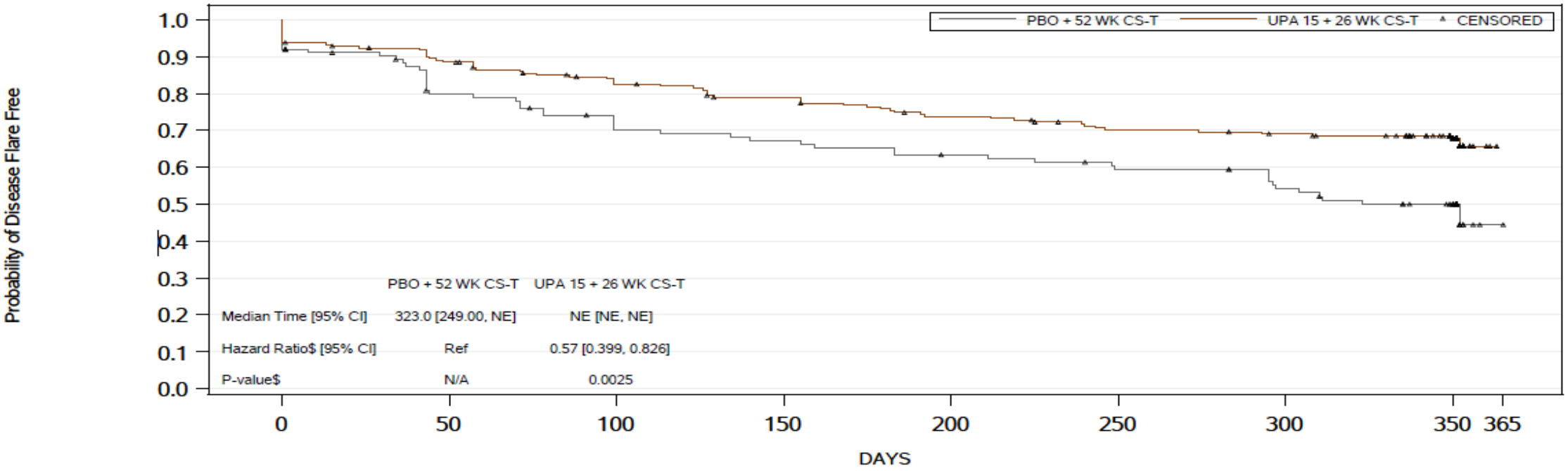
A statistically significant greater proportion of subjects achieved the primary endpoint of sustained remission (absence of GCA signs and symptoms (week 12-52) in the upadacitinib 15 mg arm (46.4% [95% CI: 39.6, 53.2]) compared with the placebo arm

Abbreviations: GCA; giant cell arteritis, CS-T; corticosteroid taper, UPA; Upadacitinib, WK week.

# Key clinical trial results – time to first flare

Return to results

Statistically significant increase in time to first flare with upadacitinib up to week 52 (ITT population)




| Hazard Ratio | 95% Confidence Interval | p-value |
|---|---|---|
| 0.57 | 0.399 – 0.826 | 0.0025 |

Abbreviations: PBO; placebo, UPA; Upadacitinib, CS-T, corticosteroid taper, WK; week

# How company incorporated evidence into model

Input and evidence sources

| Input | Assumption and evidence source |
|---|---|
| **Baseline characteristics** | SELECT-GCA |
| **Time horizon** | Lifetime |
| **Cycle length** | Weekly (7 days) |
| **Treatment waning** | Treatment benefits end following treatment |
| **Utilities** | SELECT-GCA |
| **Costs** | BNF, eMIT, Reference cost collection 2023/24, PSSRU 2023, literature |
| **Resource use** | HCRU, literature |
| **Perspective** | NHS and PSS |

Back to model overview



Abbreviations: GCA; giant cell arteritis, BNF; British national formulary, eMIT; electronic market information tool, PSSRU; personal and social services research unit, HCRU; health care resource utilisation, PSS;

# Modelling of GCA flares

Return to key issue

| | Annual Prob. | 4 Wk Prob. | Incident cost | QoL |
|---|---|---|---|---|
| Aortic aneurism | 1.12% | 0.09% | £12,688 | -0.054 |
| Aortic dissection | 0.75% | 0.06% | £27,642 | -0.129 |
| Vision loss - unilateral | 15.09% | 1.25% | £7,258 | -0.040 |
| Vision loss - bilateral | 1.38% | 0.11% | £64,580 | -0.220 |
| Incident MI | 3.81% | 0.30% | £2,206 | -0.063 |
| Previous MI | .. | .. | .. | -0.037 |
| Major stroke | 14.5% | 1.19% | £25,319 | -0.101 |
| Minor stroke | 21.7% | 1.86% | £10,848 | -0.033 |

The company model converts the annual probabilities into weekly probabilities and applies them to those in flare. Total costs per incident event are applied together



Abbreviations: QoL; quality of life, Prob; probability, MI; myocardial infarction

Return to key issue slide

# CS related AE's associate with cumulative steroid dose (1/2)

Company modelled AE's associated with corticosteroids:

- Rates were derived from an external RWE study using US-based retrospective study; analysed data from 4,115 patients with GCA treated with oral corticosteroid over an exposure period of 1 to 60 months (with follow-up extending up to 5 years and a minimum of 1 year),
- Patients were stratified by their average daily corticosteroid dose into four groups risk groups (see below table)
- Applied rates from RWE source to risk categories determining annual probabilities

| Risk category | Daily mean dose in year since diagnosis | Cumulative dose* | Number |
|---|---|---|---|
| Low risk | <5mg | <1826mg | [redacted] |
| Medium risk | 5-10mg | 1826-3653mg | [redacted] |
| High risk | 10-20mg | 3653-7305mg | [redacted] |
| Very high risk | 20-40mg | 7305-14610mg | [redacted] |
| Extremely high risk | >40mg | >14610mg | [redacted] |

*company model converts the mean steroid dose in the year since diagnosis into cumulative doses by multiplying by 365.25 days

**Steroid related conditions that are permanent, annual probability, annual cost and annual quality of life effect**

| Risk group | Low | Med. | High | V. High | E.High | | |
|---|---|---|---|---|---|---|---|
| N | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Ann.Cost | QoL |
| Heart failure* | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £2,772 | -0.117 |
| Tendon rupture | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £1,342 | -0.150 |
| Hyperlipidaemia | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18 | -0.007 |
| Bone necrosis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £2,335 | -0.060 |
| Atherosclerosis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £1,157 | -0.036 |
| Osteoporosis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £76 | -0.042 |
| Glaucoma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £827 | -0.039 |

* Note that heart failure is hospitalisation for heart failure

# Subset of conditions exacerbated by steroid use: SELECT-GCA vs company market survey

Return to key issue slide

| SELECT-GCA placebo arm | | US-based retrospective study | | Ratio |
|---|---|---|---|---|
| **Sleep disorders** | [redacted] | Sleep disorders** | [redacted] | [redacted] |
| **Type 2 diabetes** | [redacted] | Type 2 diabetes* | [redacted] | [redacted] |
| **Hypertension** | [redacted] | Hypertension** | [redacted] | [redacted] |
| **GI perforation** | [redacted] | GI perforation* | [redacted] | [redacted] |
| **Ulcers** | [redacted] | Ulcer/GI bleed* | [redacted] | [redacted] |
| **Gastritis** | [redacted] | Gastritis* | [redacted] | [redacted] |
| **Sepsis** | [redacted] | Sepsis* | [redacted] | [redacted] |
| **Dyspnoea** | [redacted] | Dyspnoea* | [redacted] | [redacted] |
| **Adrenal suppression** | [redacted] | Endoc. adrenal insuff.* | [redacted] | [redacted] |
| **Serious infections** | [redacted] | Infection Hosp: | [redacted] | [redacted] |
| **Osteoporosis** | [redacted] | Osteoporosis** | [redacted] | [redacted] |
| **IOP increased** | [redacted] | Increased IOP* | [redacted] | [redacted] |
| **Glaucoma** | [redacted] | Glaucoma** | [redacted] | [redacted] |

Abbreviations: GCA; giant cell arteritis, GI; gastrointestinal, IOP; intraocular pressure, ND; not defined

Return to key issue

# Duration of transient conditions

EAG expert opinion suggests estimate of duration:

- 1 month for electrolyte disorders, infections including those requiring hospitalisation and sepsis
- 6 months for fractures, palpitations, ulcer/GI bleeds, gastritis, sleep disorders, bruising, skin thinning, impaired wound healing, Cushing's syndrome, hypertension

The EAG will apply these durations of conditions' quality of life effects, the remainder being assumed to last 1 year as per the company base case

Abbreviations: GI; gastrointestinal

# EAG model correction – minimal impacts on ICER

Return to key issue slide

| EAG corrections with minimal impacts on costs and QALYs | Impact on costs | Impact on QALYs |
|---|---|---|
| Company base case (difference in costs/QALYs) | [redacted] | [redacted] |
| 1. EAG corrected baseline cumulative steroid use in model. For relapsed group, 0 is implausible as they have an average duration of GCA of [redacted] days. | | |
| 6. Company assumes total daily steroid use is conditional on overall survival. EAG disagrees and corrects for this | [redacted] | [redacted] |
| 7. EAG applies a simple average for the cost of prednisolone rather than weighting it by market share | [redacted] | [redacted] |

# Calculation of mean daily steroid dose

Return to key issue slide

| | | | Company method | | EAG method | |
|---|---|---|---|---|---|---|
| Alive | On steroid | Dose | Mean | Total | Mean | Total |
| 100% | 50% | 40 mg | 20 mg | 20 mg | 20 mg | 20 mg |
| 50% | 25% | 40 mg | 10 mg | 30 mg | 20 mg | 40 mg |
| 30% | 15% | 40 mg | 6 mg | 36 mg | 20 mg | 60 mg |
| 10% | 5% | 40 mg | 2 mg | 38 mg | 20 mg | 80 mg |

EAG comments:

- There is debate on whether cumulative steroid dose should be based on the proportion on steroids or the proportion alive; EAG finds adding doses from different patients does not make sense.
- Company assumes only patients currently on steroids are at risk of steroid-related conditions, which EAG considers unreasonable since risks like T2DM or osteoporosis can persist after tapering.
- EAG argues that if cumulative steroid dose determines risk, it should not drop to zero after tapering; some conditions might need modelling based on prior year's cumulative dose.
- EAG concludes cumulative steroid dose should apply to the surviving cohort, with all survivors considered at risk

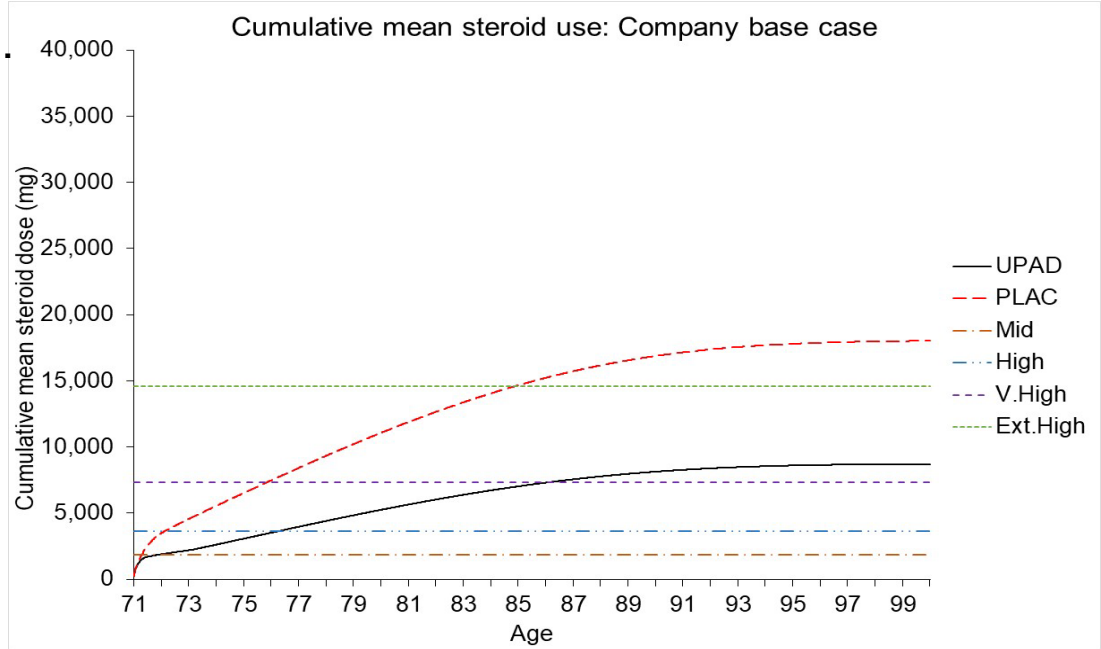


Abbreviations: T2DM; type 2 diabetes mellitus

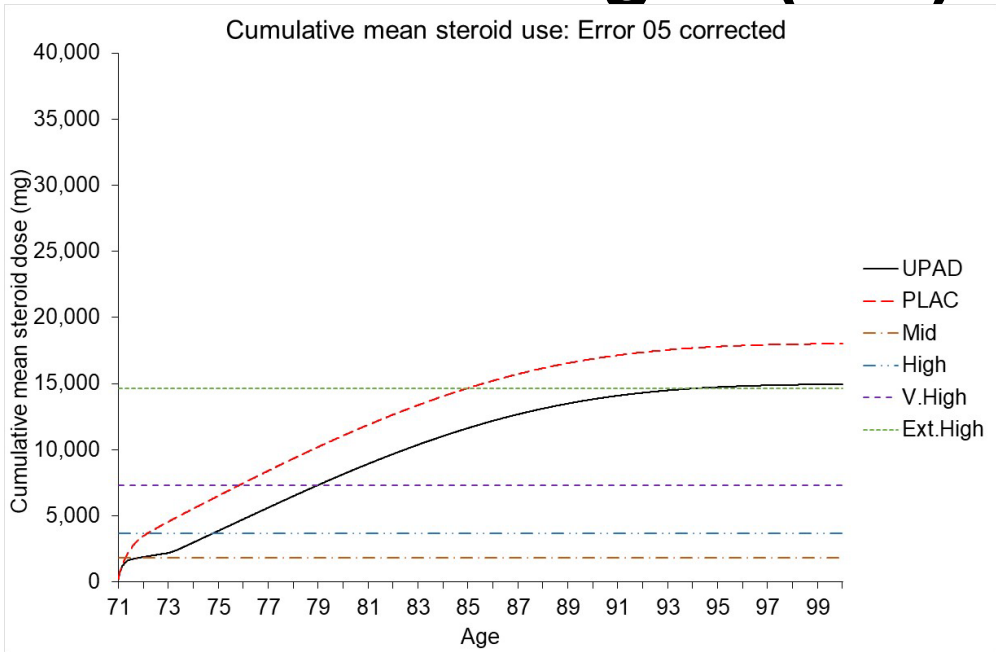
Return to key issue slide

# Cumulative mean steroid dose – EAG changes (ITT)

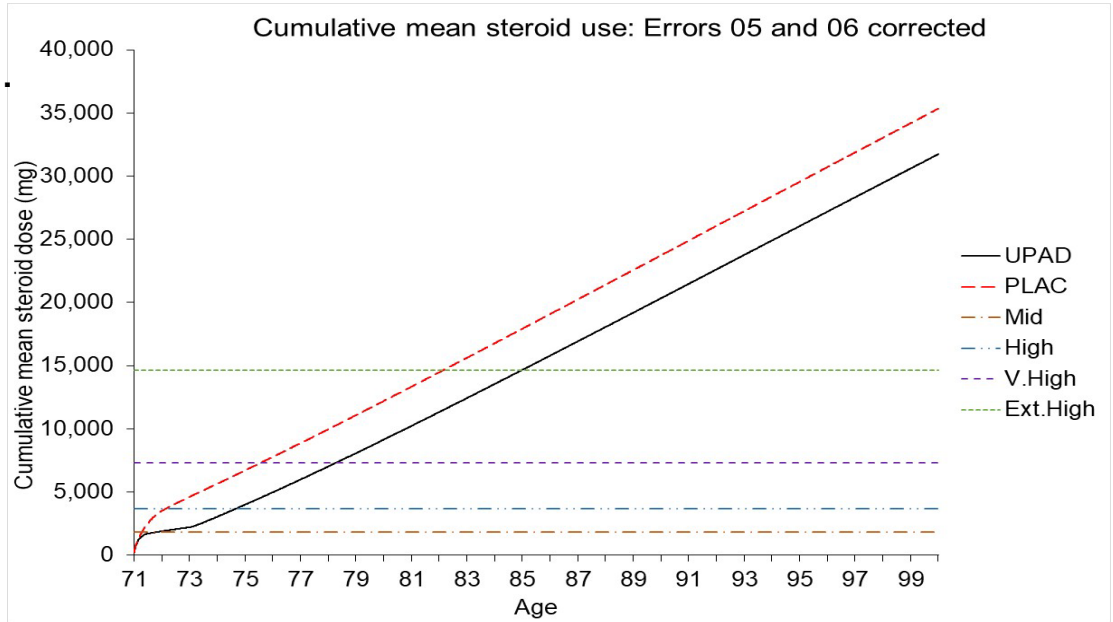
1.




2.




3.




EAG:

- Image 1. The increasing separation between the 2 curves in company base case is due to the retention of the upadacitinib 26 week tapering schedule after cessation of upadacitinib treatment.
- Image 2. Shows EAG correction 5 (switch to 56-week taper
- Image 3. Shows EAG correction 5 + 6 (cumulative steroid dose should apply to the surviving cohort, with all survivors considered at risk

## Event costs changes in EAG base case

Return to key issue slide

| Complication | Company cost | Company source | EAG Cost | EAG source |
|---|---|---|---|---|
| Minor stroke* | £10,848 | Inpatient stay - NHS reference costs | £2,170 | Company used same source as major - EAG unreasonable so reduces costs |
| Major stroke* | £25,319 | Inpatient stay - NHS reference costs | £36,274 | Costs likely higher due large rehab costs – uses literature source |
| Glaucoma | £845 | NHS reference costs | £405 | Study of 5 NHS hospital glaucoma clinics |
| Hypertension | £759 | Inpatient stay - NHS reference costs | £56 | Cost 1x GP appointment and ACE inhibitor |
| Ulcer/GI bleed | £1,907 | Inpatient stay - NHS reference costs | £585 | Assumes arbitrarily: 10% GI bleeds requiring hospitalisation; rest require GP appt and omeprazole) |
| Adrenal insufficiency | £1,922 | Chauhan et al, an industry sponsored study of UK patients | £1351 | Removes productivity losses |
| Severe infection | £4263 | averaging a range of NHS reference costs for non - elective inpatient long stay that include infections in their descriptors | £2150 | Accounts for inpatient short stay as well as long stay |
| Dyspnoea | £1667 | Inpatient stay - NHS reference costs | £417 | Assumes 1 GP visit and 4 visits to pulmonary rehab |
| Sleep disorders | £970 | Inpatient stay - NHS reference costs | £417 | Assumes same as dyspnoea – but may be too high |

*This is total cost for 5 years